IMIDAZOPYRIDINE COMPOUNDS AS 5-HT$_4$ RECEPTOR AGONISTS

Related Applications

This application claims benefit of priority under 35 U.S.C 119(e) to U.S. Provisional Application No. 60/412,485 filed on September 20, 2002, which is herein incorporated in its entirety by reference.

Technical Field

This invention relates to novel imidazopyridine compounds. These compounds have 5-HT$_4$ receptor agonist binding activity, and thus are useful for the treatment of or prevention of gastroesophageal reflux disease, gastrointestinal disease, gastric motility disorder, non-ulcer dyspepsia, functional dyspepsia, irritable bowel syndrome, constipation, dyspepsia, esophagitis, gastroesophageal disease, nausea, central nervous system disease, alzheimers disease, cognitive disorder, emesis, migraine, neurological disease, pain, ischaemic stroke, anxiety, cardiovascular disorder or the like, in mammalian, especially human. The present invention also relates to a pharmaceutical composition comprising the above compounds.

Background Art

Serotonin (5-HT) receptors are known to have a plurality of subtypes such as 5-HT$_1$, 5-HT$_2$, 5-HT$_3$ and 5-HT$_4$. These 5-HT$_4$ receptors are disclosed in, for example, European Journal of Pharmacology 146 (1988), 187-188, and Naunyn-Schmiedeberg's Arch. Pharmacol. (1989) 340:403-410.

5-HT$_4$ receptor modulators (e.g., agonists and antagonists) are found to be useful for the treatment of a variety of diseases such as gastroesophageal reflux disease, gastrointestinal disease, gastric motility disorder, non-ulcer dyspepsia, functional dyspepsia, irritable bowel syndrome, constipation, dyspepsia, esophagitis, gastroesophageal disease, nausea, central nervous system disease, alzheimers disease, cognitive disorder, emesis, migraine, neurological disease, pain, and cardiovascular disorders such as cardiac failure and heart arryhthmia (See *TiPs*, 1992, 13, 141; Ford A. P. D. W. et al., *Med. Res. Rev.*, 1993, 13, 633; Gullikson G.

EXPRESS MAIL NO. EV301907109 US

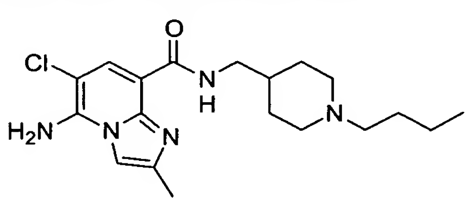
W. et al., *Drug Dev. Res.,*1992, 26, 405; Richard M. Eglen et al, *TiPS*, 1995, 16, 391; Bockaert J. Et al., *CNS Drugs,* 1, 6; Romanelli M. N. et al., *Arzheim Forsch./Drug Res.,* 1993, 43, 913; Kaumann A. et al., *Naunyn-Schmiedeberg's.* 1991, 344, 150; and Romanelli M. N. et al., *Arzheim Forsch. /Drug Res.,* 1993, 43, 913).

A variety of imidazopyridine compounds have been known as 5HT receptor antagonists or agonists. For example, Japanese Patent Publication Laid-Open No. H01-258,674 and H02-643,274 disclose imidazopyridine compounds as 5HT receptor antagonists. WO 96/05166 discloses imidazopyridine compounds as $5HT_4$ agonists. WO92/15593; USP 5,260,303; USP 5,604,239; USP 5,591,749; USP 5,219,850; USP 5,434,161; USP 5,137,893; USP 5,196,547; and EP 504679 describe a variety of imidazopyridine compounds as $5HT_3$ receptor antagonists. WO94/08998 discloses imidazopyridine compounds as $5HT_4$ receptor antagonists.

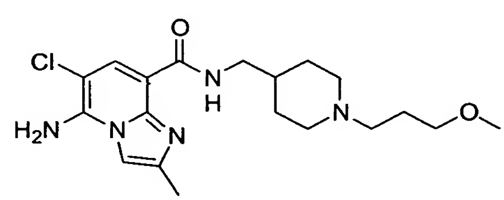
Also, imidazopyridine compounds synthesized for different uses are described in JP2001/6877; WO01/5763; WO 99/50247; WO 97/27852、WO 9738665 and EP 274867.

It would be desirable if there were provided $5HT_4$ receptor agonists which have more $5HT_4$ receptor agonist activities.

A variety of imidazopyridine 5-HT_4 receptor modulators compounds were disclosed in US Application Number 60/343,371, filed on October 22, 2001. Especially, compounds represented by the following formula is disclosed in US Application Number 60/343,371:



Compound A



Compound B

QT prolongation is known to have a potential liability to produce fatal cardiac arrhythmias of Torsades de Pointes (TdP). The ability to prolong the

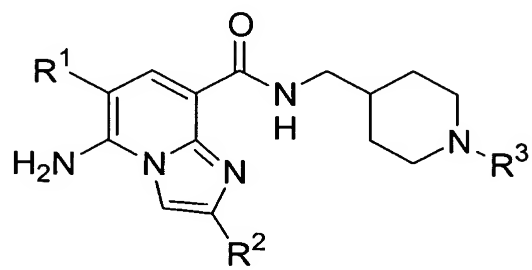
cardiac action potential duration was identified as being due to an action at the HERG potassium channel. For example, drugs withdrawn from the market due to QT prolongation, such as Cisapride and Terfenadine, are known to be potent HERG potassium channel blocker (Expert Opinion of Pharmacotherapy.; 2, pp. 947-973, 2000). Therefore, it would be desirable if there were provided a novel $5HT_4$ selective agonist useful for the treatment of a variety of diseases such as gastroesophageal reflux disease, gastrointestinal disease, gastric motility disorder, non-ulcer dyspepsia, functional dyspepsia, irritable bowel syndrome, constipation, dyspepsia, esophagitis, gastroesophageral disease, nausea, central nervous system disease, alzheimers disease, cognitive disorder, emesis, migraine, neurological disease, pain, and cardiovascular disorders such as cardiac failure and heart arrhythmia, by systemic administration and with reduced inhibitory activity at HERG potassium channel.

Brief Disclosure of the Invention

It has now surprisingly been found that compounds broadly covered by US Application Number 60/343,371 are $5HT_4$ selective agonists useful for the treatment of a variety of diseases such as gastroesophageal reflux disease, gastrointestinal disease, gastric motility disorder, non-ulcer dyspepsia, functional dyspepsia, irritable bowel syndrome, constipation, dyspepsia, esophagitis, gastroesophageral disease, nausea, central nervous system disease, alzheimers disease, cognitive disorder, emesis, migraine, neurological disease, pain, and cardiovascular disorders such as cardiac failure and heart arrhythmia, by systemic administration and with reduced inhibitory activity at HERG channel. Inhibitory activity at HERG channel was estimated from affinity for HERG type potassium channel was investigated by checking [^{3}H]dofetilide binding, which can predict inhibitory activity at HERG channel (Eur. J. Pharmacol., 430, pp147-148, 2001). Selected compounds with low [^{3}H]dofetilide binding activity were evaluated in I_{HERG} assay to check activity at HERG channel. Introducing a branched chain group to nitrogen atom in piperidine ring contributed to potent 5-HT_4 receptor agonist activities with reduced inhibitory activity at HERG channel. The compounds of the present invention may show less

toxicity, good absorption, distribution and less drug-drug interaction, and have metabolic stability.

The present invention provides a compound of the following formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

R^1 represents a hydrogen atom or a halogen atom;

R^2 represents a methyl group or an ethyl group;

R^3 represents a branched alkyl group having from 3 to 6 carbon atoms or an alkyl group having from 3 to 6 carbon atoms substituted by an alkoxy group having from 1 to 6 carbon atoms;

with the proviso that when the terminal carbon atom of said alkyl group of R^3 is substituted by said alkoxy group, said alkyl group is a branched alkyl group.

The imidazopyridine compounds of this invention have 5-HT_4 receptor agonistic activities, and are thus useful for the treatment or prevention of disease conditions mediated by 5-HT_4 receptor activities with reduced inhibitory activity at HERG channel.

Thus, the present invention provides a pharmaceutical composition for the treatment of disease conditions mediated by 5-HT_4 receptor activities, in a mammalian subject, which comprises administering to said subject a therapeutically effective amount of a compound of formula (I).

Further, the present invention also provides a pharmaceutical composition for the treatment of gastroesophageal reflux disease, gastrointestinal disease, gastric motility disorder, upper gut motility disorder, non-ulcer dyspepsia, functional

dyspepsia, irritable bowel syndrome, constipation, dyspepsia, esophagitis, gastroesophageral disease, nausea, central nervous system disease, alzheimers disease, cognitive disorder, emesis, migraine, neurological disease, pain, ischaemic stroke, anxiety, cardiovascular disorders such as cardiac failure and heart arryhthmia, or the like, which comprises a therapeutically effective amount of the imidazopyridine compound of formula (I) or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

Also, the present invention provides a method for the treatment of disease conditions mediated by 5-HT_4 receptor activities, in a mammalian subject, which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. Further, the present invention provides a method for the treatment of the disease conditions as mentioned above. Furthermore, the present invention provides use of the compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prevention of disease conditions mediated by 5-HT_4 receptor activity, in a mammalian subject. The conditions mediated by 5-HT_4 receptor activity are those diseases or disorders described as above.

Detailed Description of the Invention

As used herein, unless indicated otherwise, the article "**a**" or "**an**" refers to both the singular and plural form of the object to which it refers.

As used herein, the term "**halogen**" means fluoro, chloro, bromo and iodo, preferably fluoro or chloro.

As used herein, the term "**alkyl**" means straight or branched chain saturated radicals, including, but not limited to methyl, ethyl, *n*-propyl, *iso*propyl, *n*-butyl, *iso*-butyl, *secondary*-butyl, *tertiary*-butyl, *iso*-pentyl, *neo*-pentyl, *tertiary*-pentyl or *iso*-hexyl.

As used herein, the term "**branched alkyl**" means branched chain saturated radicals, including, but not limited to *iso*propyl, *iso*-butyl, *secondary*-butyl, *tertiary*-butyl, *iso*-pentyl, *neo*-pentyl, *tertiary*-pentyl or *iso*-hexyl.

As used herein, the term "**alkoxy**" means alkyl-O-, including, but not limited to methoxy, ethoxy, *n*-propoxy, *iso*propoxy, *n*-butoxy, *iso*-butoxy, *secondary*-butoxy, *tertiary*-butoxy.

The term "**treating**", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment" as used herein refers to the act of treating, as "treating" is defined immediately above.

As used herein, the term "**modulator**" means compounds, agonists, antagonists, ligands, substrates and enzymes, which directly or indirectly affect regulation of the receptor activity.

In the compounds of formula (I), $\mathbf{R^1}$ represents preferably, a hydrogen atom or a chlorine atom; more preferably a chlorine atom.

In the compounds of formula (I), $\mathbf{R^3}$ represents preferably an iso-butyl group, a tert-butylethyl group; and said alkyl group in $\mathbf{R^3}$ is unsubstituted or is substituted by a methoxy group.

Preferred individual compound of this invention is:
5-amino-*N*-[(1-isobutylpiperidin-4-yl)methyl]-2-methylimidazo[1,2-*a*]pyridine-8-carboxamide or a salt thereof.

Preferred individual compound of this invention is:
5-amino-6-chloro-*N*-{[1-(3,3-dimethylbutyl)piperidin-4-yl]methyl}-2-ethylimidazo[1,2-*a*]pyridine-8-carboxamide or a salt thereof.

Preferred individual compound of this invention is:
5-amino-6-chloro-2-ethyl-*N*-{[1-(2-methoxy-2-methylpropyl)piperidin-4-yl]methyl}imidazo[1,2-*a*]pyridine-8-carboxamide or a salt thereof.

Preferred individual compound of this invention is:
5-amino-6-chloro-2-methyl-*N*-{[1-(2-methoxy-2-methylpropyl)piperidin-4-yl]methyl}imidazo[1,2-*a*]pyridine-8-carboxamide or a salt thereof.

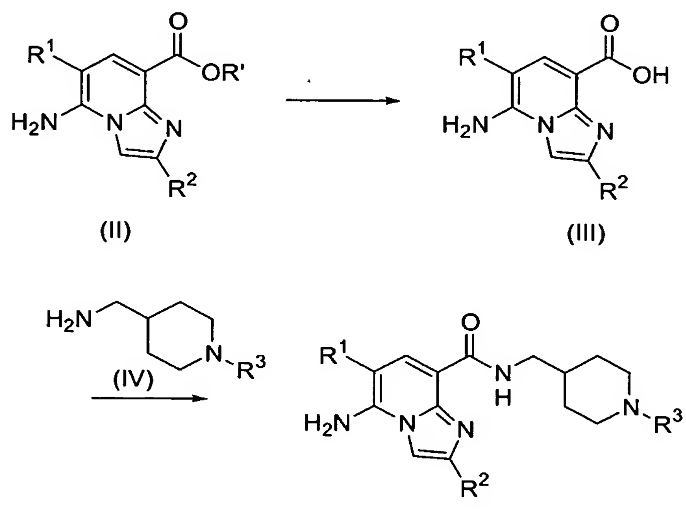
Preferred individual compound of this invention is:
5-amino-6-chloro-*N*-[(1-isobutylpiperidin-4-yl)methyl]-2-methylimidazo[1,2-

a]pyridine-8-carboxamide or a salt thereof.

General Synthesis

The imidazopyridine compounds of formula (I) of this invention may be prepared by a variety of synthetic methods. Unless indicated otherwise, all variables (e.g. R^1, R^2 and R^3) are defined as set forth herein. For example, the imidazopyridine compounds of formula (I), may be prepared by saponification of a carboxylate compound (II) to obtain a corresponding carboxylic acid compound (III), followed by a coupling reaction of the compound (III) with an amine compound (IV), as indicated in the following Scheme 1.

Scheme 1:



(I)

wherein R' is C_{1-3} alkyl or benzyl.

In Scheme 1, the carboxylate compound (II) may be first subjected to saponification of the ester residue at the 8-position of the imidazopyridine ring, followed by acidification to afford a corresponding carboxylic acid (III). Then, the compound (III) may be coupled with the amine compound (IV) to give an imidazopyridine compound (I).

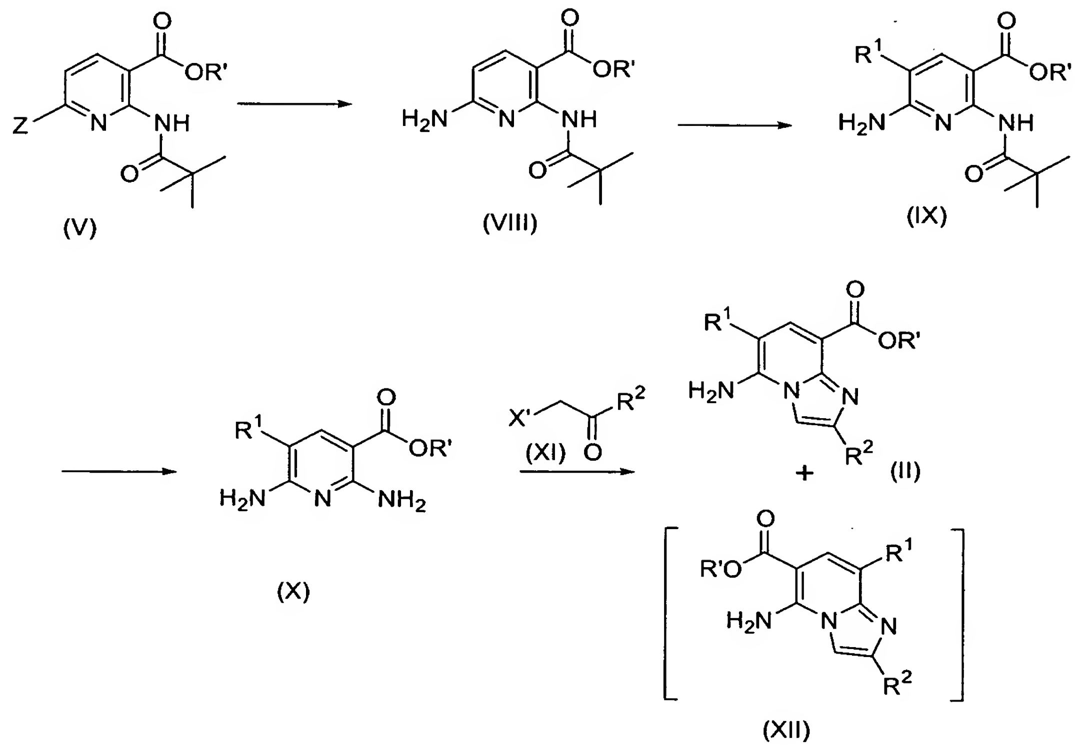
The saponification and the acidification may be carried out by conventional procedures. In a typical procedure, the saponification is carried out by treatment with sodium hydroxide or lithium hydroxide in a suitable reaction-inert solvent.

Suitable solvents include, for example, alcohols such as methanol, ethanol, propanol, butanol, 2-methoxyethanol, and ethylene glycol; ethers such as tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), and 1,4-dioxane; halogenated hydrocarbons such as chloroform, dichloroethane, and 1,2-dichloroethane; amides such as *N,N*-dimethylformamide (DMF) and hexamethylphospholictriamide; and sulfoxides such as dimethyl sulfoxide (DMSO). This reaction may be carried out at a temperature in the range from -20 to 100°C, usually from 20°C to 65°C for 30 minutes to 24 hours, usually 60 minutes to 10 hour. In a typical procedure, the acidification is carried out by treatment with diluted hydrochloric acid or 10% aqueous citric acid in a suitable reaction-inert solvent such as water at a temperature in the range from -20 to 65°C, usually from 0°C to 30°C for 30 minute to 10 hour, usually 30 minutes to 2 hours.

The coupling reaction may be carried out in the presence of a suitable condensation agent in a reaction-inert solvent. Suitable condensation agents include 1,1'-carbonyldiimidazole (CDI), diisopropylcarbodiimide (DIC), dicyclohexylcarbodiimide (DCC), water soluble carbodiimide (WSC), 2-ethoxy-N-ethoxycarbonyl-1,2-dihydroquinoline, benzotriazol-1-yloxy-tris(dimethylamino) phosphonium hexafluorophosphate (BOP), diethyl azodicarboxylate-triphenylphosphine, diethylcyanophosphonate (DEPC), diphenylphosphorylazide (DPPA), bromotripyrrolidino phosphonium hexafluorophosphate (PyBrop[trademark]), bis(2-oxo-3-oxazolidinyl) phosphinic chloride (BOPCl), benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP), 2-(1-H-benzotriazole-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate (HBTU) and ethyl chloroformate. Suitable reaction-inert solvents include aqueous or non-aqueous organic solvents such as THF, DMF, 1,4-dioxane, acetone, DME and acetonitrile; and halogenated hydrocarbons such as chloroform, dichloromethane and 1,2-dichloroethane (preferably dichloromethane). This reaction may be carried out at a temperature in the range from -20 to 80°C, usually from 0°C to 30°C for 30 minutes to 100 hours, usually 5 hours to 24 hours.

Scheme 2:

The carboxylate compounds (II) used as starting materials in Scheme 1 may be prepared in the following reaction steps.



In Scheme 2, a nicotinate compound (V) wherein R' is C_{1-3} alkyl or benzyl and Z is halogen ; and the amino group is protected by a pivaloyl group, may be reacted with an ammonia to obtain a compound (VIII). This reaction is generally carried out in a sealed tube. This reaction can be carried out in a suitable reaction-inert solvent such as methanol, ethanol, propanol, butanol, 2-methoxyethanol and THF. This reaction may be carried out at a temperature in the range from 30 to 150°C, usually from 50°C to 100°C for 30 minutes to 24 hours, usually 30 minutes to 12 hours. When R^1 is halo, the compound (VIII) is treated with halogen or N-halogenated succimide or SELECTFLUOR™ (1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate commercially available from

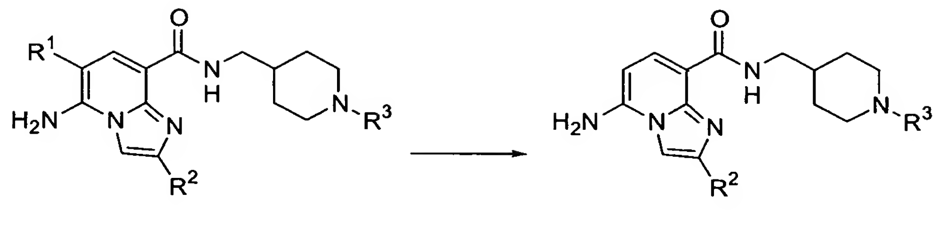
Aldrich) under appropriate conditions, to obtain a compound (IX) wherein R^1 is halo. This reaction can be carried out in a suitable reaction-inert solvent such as carboxylic acids (e.g., acetic acid, propionic acid and butylic acid); halogenated hydrocarbons such as chloroform, dichloroethane and 1,2-dichloroethane; amides such as DMF and hexamethylphospholictriamide; sulfoxides such as DMSO; acetonitrile; benzene, toluene, xylene; and pyridine. This reaction may be carried out at a temperature in the range from 0 to 80°C, usually from 25 to 70°C for 5 minutes to 24 hours, usually 15 minutes to 8 hours. Then, the compound (IX) may be subject to deprotection of an amino-protecting group, to obtain a compound (X). The deprotection may be carried out in the presence of base (e.g., potassium tert-butoxide, sodium ethoxide and sodium hydroxide) or acids (e.g., hydrochloric acid and sulfuric acid). The deprotection can be carried out in a suitable reaction-inert solvent such as methanol at a temperature in the range from 25 to 80°C, usually from 50 to 65°C for 10 minutes to 24 hours, usually 30 minutes to 10 hours.

Then, the compound (X) may be reacted with a compound (XI) wherein X' is halogen, to obtain a compound (II) and a compound (XII). This reaction can be carried out in the presence of 2-halogenated aldehyde or 2-halogenated ketone (compound (XI)) in a suitable reaction-inert solvent such as methanol, ethanol, propanol and butanol at a temperature in the range from 25 to 120°C, usually from 50°C to 65°C for 8 hours to 72 hours, usually 8 hours to 24 hours. The resulting mixture of the compound (II) and the compound (XII) may be subjected to conventional separation techniques to obtain the compound (II). Suitable conventional separation techniques include silica gel column chromatography.

In addition, starting compounds of formula (V) are known or may be prepared from a known compound according to procedures known to those skilled in the art.

Scheme 3:

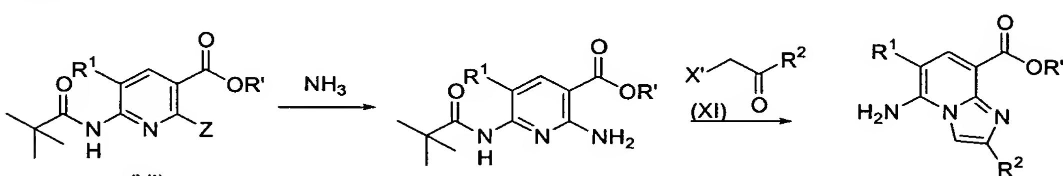
Compounds (I') (Compound (I) wherein R^1 is hydrogen) can be prepared by subjecting a compound (I) wherein R^1 is halo, to catalytic hydrogenation.



(I) (I')

In Scheme 3, the catalytic hydrogenation can be carried out in the presence of hydrogen or hydrogen source such as ammonium formate, triethylsilane and a suitable metal containing catalysts such as palladium, platinum, nickel, platinum oxide and rhodium in a suitable reaction-inert solvent such as methanol. The preferred catalyst is palladium on carbon. This hydrogenation can be carried out at a temperature in the range from 20 to 100°C, usually from 25°C to 80°C for 5 minutes to 48 hours, usually 30 minutes to 2 hours.

Scheme 4:



(VI) (VII) (II)

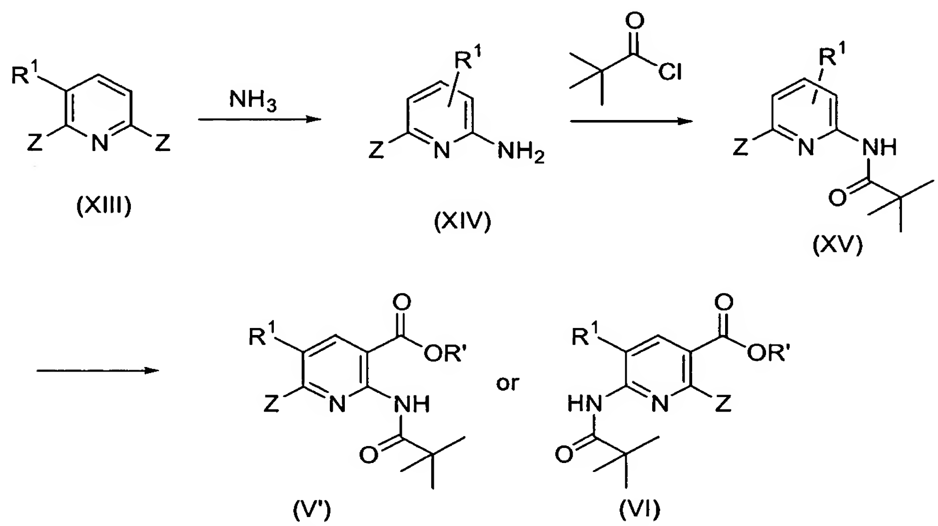
where R', Z and X' are each as set forth in Scheme 2.

In scheme 4, the compound (VI) may be reacted with an ammonia water to obtain a compound (VII). This reaction is generally carried out in a sealed tube. This reaction can be carried out in a suitable reaction-inert solvent. Suitable solvents include, for example, alcohols such as methanol, ethanol, propanol, butanol, 2-methoxyethanol and ethylene glycol; ethers such as THF, DME, diethyl ether, diisopropyl ether, diphenyl ether and 1,4-dioxane; halogenated hydrocarbons such as chloroform, dichloroethane and 1,2-dichloroethane; amides such as DMF and hexamethylphospholictriamide; sulfoxides such as DMSO; acetonitrile; benzene, toluene, xylene; and pyridine. This reaction may be carried out at a temperature in

the range from 30 to 150°C, usually from 50°C to 100°C for 30 minutes to 24 hours, usually 30 minutes to 12 hours. Compounds (II) may be prepared by reacting a compound (VII) with the compound (XI) under appropriate conditions. This reaction can be carried out in a suitable reaction-inert solvent such as methanol. This reaction may be carried out at a temperature in the range from 25 to 65°C, usually from 50°C to 65°C for 30 minutes to 48 hours, usually 30 minutes to 12 hours.

Scheme 5 :

The nicotinate compounds (V') and (VI) used as starting materials in Scheme 2, 4 and 6 may be prepared in the following reaction steps.



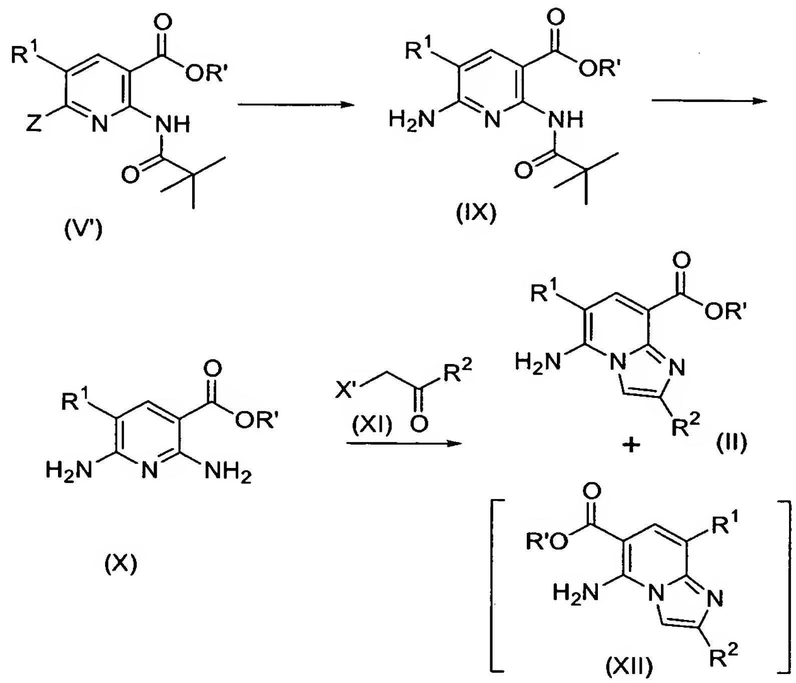
where R' is as set forth in Scheme 2.

In scheme 5, a pyridine compound (XIII) wherein Z, each of which can be the same or different, is halogen, may be reacted with an ammonia water to obtain a compound (XIV). This reaction is generally carried out in a sealed tube. This reaction may be carried out at a temperature in the range from 50 to 200°C, usually from 100°C to 160°C for 30 minutes to 24 hours, usually 30 minutes to 12 hours. The compound (XIV) is treated with acyl chloride, for example, pivaloyl chloride in the presence of base, such as diisopropylethylamine, triethylamine, pyridine and lutidine to obtain a mixture of compound (XV). This reaction can be carried out in a suitable reaction-inert solvent. Suitable solvents include, for example,

halogenated hydrocarbons such as chloroform, dichloroethane and 1,2-dichloroethane. This reaction may be carried out at a temperature in the range from -20 to 50°C, usually from -10°C to 30°C for 30 minutes to 24 hours, usually 30 minutes to 10 hours. The compound (XV) is treated with alkaline metal, for example, n-BuLi followed by alkyl haloformate, for example, ethyl chloroformate or carbobenzyloxychloride to obtain a compound (V') and (VI). This reaction can be carried out in a suitable reaction-inert solvent. Suitable solvents include, for example, ethers such as THF, DME, diethyl ether, diisopropyl ether, diphenyl ether and 1,4-dioxane. This reaction may be carried out at a temperature in the range from -100 to 50°C, usually from -100 to 20°C for 5 minutes to 24 hours, usually 15 minutes to 8 hours. In addition, starting compounds of formula (XIII) are known or may be prepared from a known compound according to procedures known to those skilled in the art, for example, *Helv. Chim. Acta* **(1976)**, 59, 229-35, *J. Chem. Soc., Perkin Trans. 1* **(1996)**, 519-24 and *J. Chem. Soc., Chem. Commun.* **(1988)**, 1482-3.

Scheme 6 :

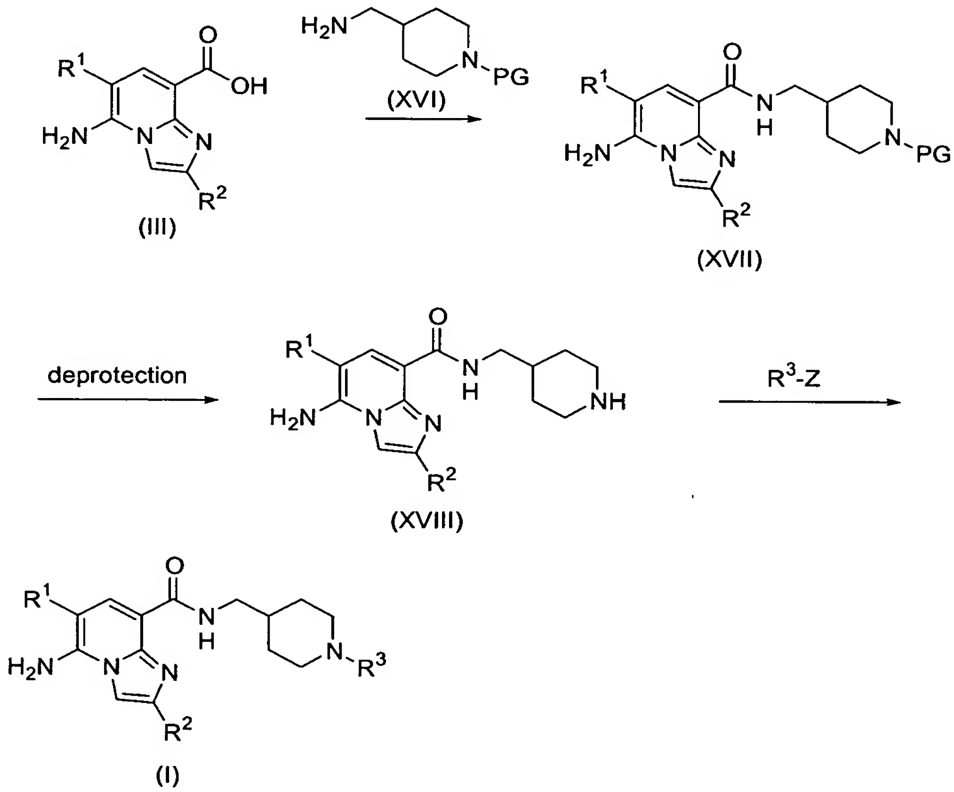
The carboxylate compounds (II) used as starting materials in Scheme 1 may be prepared in the following reaction steps.



In Scheme 6, a nicotinate compound (V') wherein R' is C_{1-3} alkyl or bezyl and Z, each of which can be the same or different, is halogen ; and the amino group is protected by a pivaloyl group, may be reacted with an ammonia to obtain a compound (IX). This reaction is generally carried out in a sealed tube. This reaction can be carried out in a suitable reaction-inert solvent such as methanol, ethanol, propanol, butanol, 2-methoxyethanol and tetrahydrofuran (THF). This reaction may be carried out at a temperature in the range from 30 to 150°C, usually from 50°C to 100°C for 30 minutes to 24 hours, usually 30 minutes to 12 hours. Then, the compound (IX) may be subject to deprotection of an amino-protecting group, to obtain a compound (X). The deprotection may be carried out in the presence of base (e.g., potassium tert-butoxide, sodium ethoxide and sodium hydroxide) or acids (e.g., hydrochloric acid and sulfuric acid). The deprotection can be carried out in a suitable reaction-inert solvent such as methanol at a temperature in the range from 25 to 80°C, usually from 50 to 65°C for 10 minutes to 24 hours, usually 30 minutes to 10 hours.

Then, the compound (X) may be reacted with a compound (XI) where X' is halogen to obtain a compound (II) and a compound (XII). This reaction can be carried out in the presence of 2-halogenated aldehyde or 2-halogenated ketone (compound (XI)) in a suitable reaction-inert solvent such as methanol, ethanol, propanol and butanol at a temperature in the range from 25 to 120°C, usually from 50°C to 65°C for 8 hours to 72 hours, usually 8 hours to 24 hours. The resulting mixture of the compound (II) and the compound (XII) may be subjected to conventional separation techniques to obtain the compound (II). Suitable conventional separation techniques include silica gel column chromatography.

Scheme 7



wherein R' is C_{1-3} alkyl, Z is halogen, and PG is a protecting group.

In Scheme 7, the carboxylic acid compound (III) may be coupled with the amine compound (XVI) to give an imidazopyridine compound (XVII). Then, the compound (XVII) may be subjected to deprotection of the protecting group of

nitrogen atom in the piperidine ring, followed by alkylation to afford an imidazopyridine compound (I').

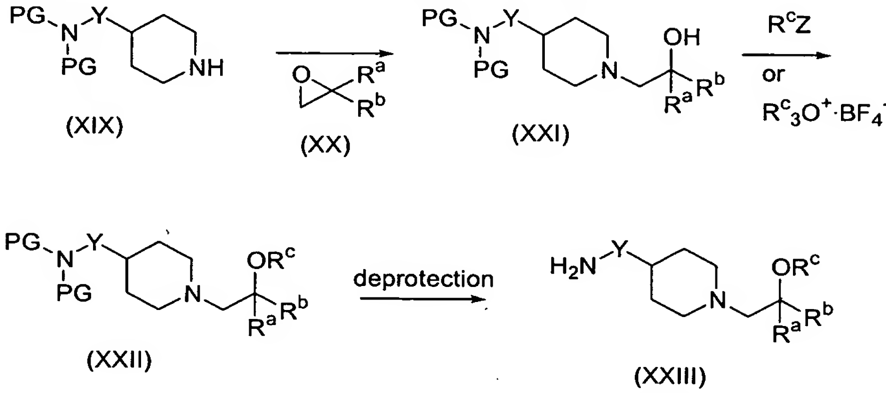
The coupling reaction may be carried out in the presence of a suitable condensation agent in a reaction-inert solvent. Suitable condensation agents include 1,1'-carbonyldiimidazole (CDI), diisopropylcarbodiimide (DIC), dicyclohexylcarbodiimide (DCC), water soluble carbodiimide (WSC), 2-ethoxy-N-ethoxycarbonyl-1,2-dihydroquinoline, benzotriazol-1-yloxy-tris(dimethylamino) phosphonium hexafluorophosphate (BOP), diethyl azodicarboxylate-triphenylphosphine, diethylcyanophosphonate (DEPC), diphenylphosphorylazide (DPPA), bromotripyrrolidino phosphonium hexafluorophosphate (PyBrop[trademark]), bis(2-oxo-3-oxazolidinyl) phosphinic chloride (BOPCl), benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP), 2-(1-H-benzotriazole-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate (HBTU) and ethyl chloroformate. Suitable reaction-inert solvents include aqueous or non-aqueous organic solvents such as THF, DMF, 1,4-dioxane, acetone, DME and acetonitrile; and halogenated hydrocarbons such as chloroform, dichloromethane and 1,2-dichloroethane (preferably dichloromethane). This reaction may be carried out at a temperature in the range from -20 to 80°C, usually from 0°C to 30°C for 30 minutes to 100 hours, usually 5 hours to 24 hours.

The obtained amino compound may be subjected to deprotection of an amino-protecting group, to obtain a compound (XVIII). The deprotection may be carried out by a number of standard procedures known to those skilled in the art (e.g., "Protection for the Hydroxy Group and the Amino Group ", in *Protective Groups in Organic Synthesis*, 2nd Edition, T. W. Greene and P.G. M. Wuts, Ed., John Wiley and Sons, Inc. 1991, pp. 10-142, 309-405). Then, alkylation of amino group in piperidine ring may be carried out under the conventional conditions. The compound may be treated with appropriate alkyl halides (R^6-Z) in the presence of a base such as diisopropylethylamine, triethylamine, pyridine, lutidine, potassium carbonate, sodium bicarbonate, sodium carbonate or the like, in a reaction inert solvent such as dichrolomethane, THF or DMF at about 0°C to about100°C for

about 5 minutes to about 48 hours.

Scheme 8 :

An amino compound (XXIII) wherein R^a and R^b are C_{1-4} alkyl and R^c is C_{1-6} alkyl, may be prepared in the following reaction steps.

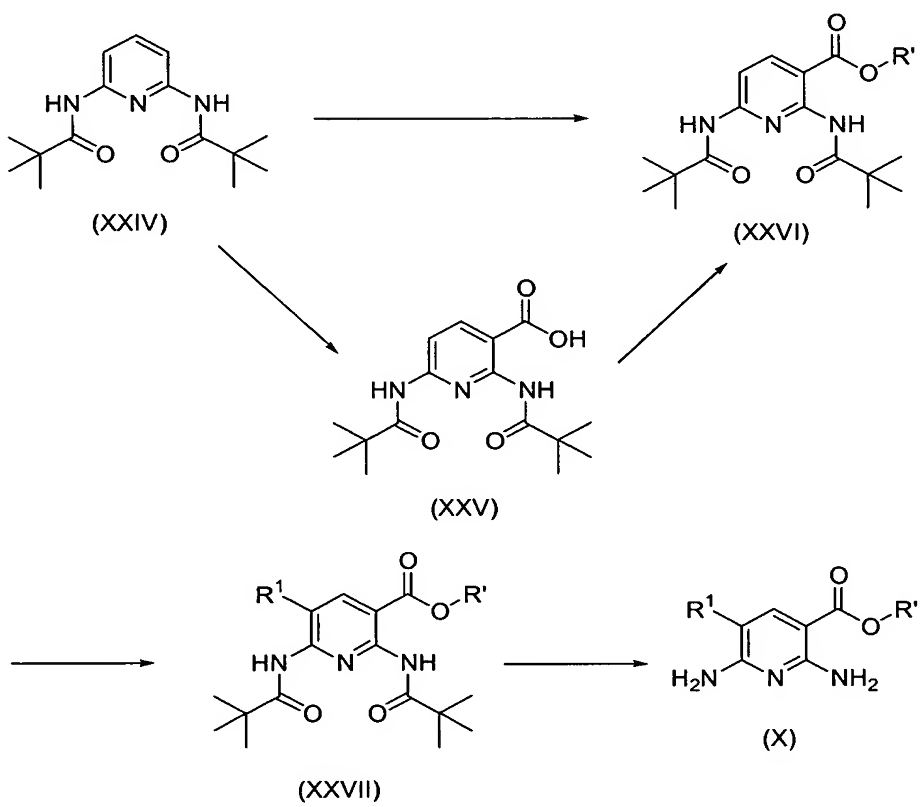


where Z is halogen, PG is a protecting group and Y is methylene.

In scheme 8, piperidine compound (XIX) may be reacted with an epoxide compound (XX) to obtain a hydroxy compound (XXI). This reaction can be carried out in a suitable reaction-inert solvent such as THF, DMF, acetonitrile, dichloromethane, 1,2-dichloroethane, DMSO, methylethylketone, methanol, ethanol, propanol, butanol, iso-butanol, sec-butanol and tert-butanol at a temperature in the range from -50 to 250°C, usually from 0°C to 200°C for 30 minutes to 100 hours, usually 1 hour to 80 hours. This reaction may be carried out in the presence of a metal halide such as sodium iodide, potassium iodide and lithium iodide. The conversion of hydroxy compound (XXI) to an alkoxy compound (XXII) may be carried out under the conventional method. The alkylation of a hydroxy group may be carried out under the conventional conditions. The compound may be treated with appropriate alkyl halides (R^6-Z) in the presence of a base such as sodium methoxide, sodium ethoxide, potassium *tert*-butoxide, sodium hydride or potassium hydride, or the like, in a reaction inert solvent such as diethyl ether, DME, DMSO, THF or DMF at about 0°C to about 200°C, usually from 0°C to 200°C, for about 5 minutes to about 100 hours, usually 1 hour to 80 hours. Alternatively, hydroxy compound (XXI) may be treated with $R^c{}_3O^+BF_4^-$ to provide the compound (XXII).

This reaction can be carried out in a suitable reaction-inert solvent such as 1,2-dichloromethane, dichloroethane, benzene, toluene and nitromethane at a temperature in the range from -50 to 200°C, usually from 0°C to 100°C for 30 minutes to 100 hours, usually 1 hour to 80 hours. The obtained compound (XXII) may be subjected to deprotection of an amino-protecting group, to obtain a compound (XXIII). The deprotection may be carried out by a number of standard procedures known to those skilled in the art (e.g., "Protection for the Hydroxy Group and the Amino Group ", in *Protective Groups in Organic Synthesis*, 2nd Edition, T. W. Greene and P.G. M. Wuts, Ed., John Wiley and Sons, Inc. 1991, pp. 10-142, 309-405).

Scheme 9:



The nicotinate compounds (X) may be prepared in the following reaction steps.

In scheme 9, a pyridine compound (XXIV) may be treated with n-BuLi

followed by R'COZ or R'COR' wherein R' is C_{1-3} alkyl or benzyl and Z is halogen, to obtain a compound (XXVI). This reaction can be carried out in a suitable reaction-inert solvent. Suitable solvents include, for example, ethers such as THF, DME, diethyl ether, diisopropyl ether, diphenyl ether and 1,4-dioxane. This reaction may be carried out at a temperature in the range from -100 to 50°C, usually from -100 to 20°C for 5 minutes to 24 hours, usually 15 minutes to 8 hours. Alternatively, the compound (XXVI) may be prepared from the pyridine compound (XXIV) by carboxylation followed by esterification. The pyridine compound (XXIV) may be treated with n-BuLi followed by carbon dioxide (gas or dry ice) to obtain a carboxylic acid compound (XXV). This reaction can be carried out in a suitable reaction-inert solvent. Suitable solvents include, for example, ethers such as THF, DME, diethyl ether, diisopropyl ether, diphenyl ether and 1,4-dioxane. This reaction may be carried out at a temperature in the range from -100 to 50°C, usually from -100 to 20°C for 5 minutes to 24 hours, usually 15 minutes to 8 hours. The compound (XXV) may be subjected to esterification to obtain the compound (XXVI). The esterification may be carried out by a number of standard procedures known to those skilled in the art (e.g., *Protective Groups in Organic Synthesis*, Third edition. ed. T.W.Green and P.G.M.Wuts, Wiley-Interscience., pp 373 - 377.). Typical esterification can be carried out with a suitable C_{1-3} alkylhalide or benzylhalide in the presence of a base in a suitable reaction-inert solvent. Suitable solvents include, for example, ethers such as THF, DME, diethyl ether, diisopropyl ether, diphenyl ether, DMF, DMSO, R'OH and 1,4-dioxane. Suitable bases include, for example, K_2CO_3, Cs_2CO3, $NaHCO_3$ and DBU. This reaction may be carried out at a temperature in the range from -100 to 200°C, usually from -10 to 100°C for 1 to 72 hours, usually 2 to 60 hours. The esterification also carried out with trimethylsilyldiazomethane in a suitable reaction-inert solvent. Suitable solvents include, for example, methanol, benzene and toluene. This reaction may be carried out at a temperature in the range from -100 to 200°C, usually from -10 to 100°C for 1 minute to 72 hours, usually 0.5 to 60 hours. The esterification also carried out with diazomethane in a suitable reaction-inert solvent. Suitable

solvents include, for example, diethyl ether. This reaction may be carried out at a temperature in the range from -100 to 200°C, usually from -50 to 100°C for 1 minute to 72 hours, usually 0.5 to 60 hours. Alternatively, the esterification may be carried out with R'OH, in the presence of a coupling agent and a tertiaryamine in a suitable solvent. Suitable coupling agents include, for example, DCC, WSC, diisoproopylcyanophosphonate (DIPC), BOPCl and 2,4,6-trichlorobenzoic acid chloride. Suitable tertiaryamines include, for example, diisopropylethylamine, triethylamine. Suitable solvents include, for example, DMF, THF, diethyl ether, DME, dichloromethane and 1,2-dichloroethane. This reaction may be carried out at a temperature in the range from -100 to 200°C, usually from -50 to 100°C for 1 minute to 100 hours, usually 0.5 to 80 hours. When R^1 is halo, the compound (XXVI) can be treated with halogen or N-halogenated succimide or SELECTFLUOR™ (1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate commercially available from Aldrich) under appropriate conditions, to obtain a compound (XXVII) wherein R^1 is halo. This reaction can be carried out in a suitable reaction-inert solvent such as carboxylic acids (e.g., acetic acid, propionic acid and butylic acid); halogenated hydrocarbons such as chloroform, dichloroethane and 1,2-dichloroethane; amides such as DMF and hexamethylphospholictriamide; sulfoxides such as DMSO; acetonitrile; benzene, toluene, xylene; and pyridine. This reaction may be carried out at a temperature in the range from 0 to 80°C, usually from 25 to 70°C for 5 minutes to 24 hours, usually 15 minutes to 8 hours. Then, the compound (XXVII) may be subject to deprotection of an amino-protecting group, to obtain a compound (X). The deprotection may be carried out in the presence of base (e.g., potassium tert-butoxide, sodium ethoxide and sodium hydroxide) or acids (e.g., hydrochloric acid and sulfuric acid). The deprotection can be carried out in a suitable reaction-inert solvent such as methanol at a temperature in the range from 25 to 80°C, usually from 50 to 65°C for 10 minutes to 24 hours, usually 30 minutes to 10 hours.

In addition, starting compound of formula (XXIV) is known or may be prepared from a known compound according to procedures known to those skilled

in the art, for example, *J. Am. Chem. Soc.* **(1986)**, 108(12), 3310-18.

The present invention includes salt forms of the compounds (I) as obtained above. Insofar as the imidazopyridine compounds of this invention are basic compounds, they are capable of forming a wide variety of different salts with various inorganic or organic acids.

The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned imidazopyridine base compounds of formula (I) are those which form non-toxic acid addition salts, i.e., salts containing pharmaceutically acceptable anions, such as the chloride, bromide, iodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bi-tartrate, succinate, malate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate (i.e., 1.1'-methylene-bis-(2-hydroxy-3-naphthoate). The acid addition salts can be prepared by conventional procedures.

The compounds of formula (I) of this invention may contain one or more asymmetric centers. Thus, the compounds can exist in separated (+)- and (-)-optically active forms, as well as in the racemic form thereof. The present invention includes all such forms within its scope. Individual isomers can be obtained by known methods, such as optically selective reaction or chromatographic separation in the preparation of the final product or its intermediate.

In addition, when the compounds of this invention form hydrates or solvates they are also within the scope of this invention.

The imidazopyridine compounds of this invention have 5-HT_4 receptor binding activity (e.g., agonist or antagonist activities), and thus are useful for the treatment or prevention of gastroesophageal reflux disease, gastrointestinal disease, gastric motility disorder, upper gut motility disorder, non-ulcer dyspepsia, functional dyspepsia, irritable bowel syndrome, constipation, dyspepsia, esophagitis, gastroesophageral disease, nausea, central nervous system disease, alzheimers disease, cognitive disorder, emesis, migraine, neurological disease, pain, ischaemic stroke, anxiety, cardiovascular disorders such as cardiac failure and heart arryhthmia,

or the like in mammalian, especially human.

The compounds of the invention may advantageously be employed in combination with one or more other therapeutic ingredients selected from an antibiotic, anti-fungal and anti-viral agent.

Method for assessing biological activities:

The 5-HT_4 receptor binding affinities of the compounds of this invention are determined by the following procedures.

Membrane Preparation

Pig heads were supplied from an abattoir. Striatal tissues were dissected, weighed and homogenized in 15 volumes of 50 mM ice-cold HEPES (pH 7.5) in a Polytron homogenizer (30 sec at full speed). Suspension was centrifuged at 48,000g and 4°C for 15 min. The resulting pellet was resuspended in an appropriate volume of 50 mM ice-cold HEPES, dispensed into aliquots and stored at -80°C until use.

Bovine heads were also supplied from an abattoir. Striatal tissues were dissected, weighed and homogenized in 20 volumes of 50 mM ice-cold Tris-HCl (pH 7.4) in a Polytron homogenizer (30 sec at full speed). Suspension was centrifuged at 20,000g and 4°C for 30 min. The resulting pellet was resuspended in 15 volumes of 50 mM ice-cold Tris-HCl, homegenized and centrifuged again in the same way. The final pellet was resuspended in an appropriate volume of 50 mM Tris-HCl, dispensed into aliquots and stored at -80°C until use.

Cerebral cortical tissues were removed from male Sprague-Dawley (SD) rats (Japan SLC), weighed and placed in 10 volumes of 50 mM ice-cold Tris-HCl (pH 7.5). This was homogenized in a Polytron homogenizer (30 sec at full speed) and subsequently centrifuged at 48,000g and 4°C for 15 min. The resulting pellet was resuspended in 50 mM ice-cold Tris-HCl, homegenized and centrifuged again in the same way. The final pellet was resuspended in an appropriate volume of 50 mM Tris-HCl, dispensed into aliquots and stored at -80°C until use.

The protein concentrations of homogenates were determined by Bradford method or BCA protein method (Pierce) with BSA as a standard.

Binding assays

Affinity of compounds for pig or bovine 5-HT4 and rat 5-HT3 receptors were assessed with using radiolabeled specific ligands, GR 113808 ({1-[2-(methylsulfonyl)ethyl]-4-piperidinyl}[methyl-^{3}H]-1*H*-indole-3-carboxylate) and BRL 43694 (1-Methyl-*N*-(9-[methyl-^{3}H]-9-azabicyclo[3.3.1]non-3-yl)-1*H*-indazole-3-caboxamide). Compounds were incubated with 25-100 pM of [^{3}H]-GR 113808 (Amersham) and 0.6-1 mg protein of pig or bovine striatal membranes suspended in a final volume of 0.8-1 ml of 50 mM Tris-HCl (pH 7.5). Nonspecific binding was determined with 10-50 μM 5-HT. The binding of 0.3 nM [^{3}H]-BRL 43694 (NEN) was measured using 400 μg protein of rat cortical membranes suspended in a final volume of 500 μl of 50 mM Tris-HCl (pH 7.5). Nonspecific binding was determined with 10 μM 5-HT.

The plates were incubated at room temperature on a plate shaker for 30min. The assays were stopped by rapid filtration using a Brandell cell harvester through Wallac-B filters pre-soaked in 0.2% poly(ethylenimine) at 4°C for 60-90min. The filters were washed three times with 1 ml of ice-cold 50 mM HEPES, and were dried in a microwave or at room temperature. They were bagged and heated with meltilex scintillant (Wallac) or soaked in BetaplateScint (Wallac). Receptor-bound radioactivity was quantified using Big-spot counter, Betaplate counter (Wallac) or LS counter (Packard).

Human 5-HT4 binding

Human 5-$HT_{4(d)}$ transfected HEK293 cells were prepared and grown in-house. The collected cells were suspended in 50 mM HEPES (pH 7.4 at 4°C) supplemented with protease inhibitor cocktail (Boehringer, 1:1000 dilution) and homogenized using a hand held Polytron PT 1200 disruptor set at full power for 30 sec on ice. The homogenates were centrifuged at 40,000 x g at 4 °C for 30 min. The pellets were then resuspended in 50 mM HEPES (pH 7.4 at 4 °C) and centrifuged once more in the same manner. The final pellets were resuspended in an appropriate volume of 50 mM HEPES (pH 7.4 at 25 °C), homogenized, aliquoted and stored at -80°C until use. An aliquot of membrane fractions was used for protein concentration

determination using BCA protein assay kit (PIERCE) and ARVOsx plate reader (Wallac).

For the binding experiments, 25 μl of test compounds were incubated with 25 μl of [^{3}H]-GR113808 (Amersham, final 0.2 nM) and 150 μl of membrane homogenate and WGA-SPA beads (Amersham) suspension solutions (10 μg protein and 1mg SPA beads/well) for 60 minutes at room temperature. Nonspecific binding was determined by 1 μM GR113808 (Tocris) at the final concentration. Incubation was terminated by centrifugation at 1000 rpm. Receptor-bound radioactivity was quantified by counting with MicroBeta plate counter (Wallac).

Functional Assay:

The presence of 5-HT_4 receptors in the rat oesophagus and the ability to demonstrate partial agonism in the TMM preparation are reported in the literature (See G.S. Baxter et al. Naunyn-Schmiedeberg's Arch Pharmacol (1991) 343: 439-446; M. Yukiko et al. JPET (1997) 283: 1000-1008; and J.J. Reeves et al. Br. J. Pharmacol. (1991) 103: 1067-1072). More specifically, partial agonist activity can be measured according to the following procedures.

Male SD rats (Charles River) weighing 250-350g were stunned and then killed by cervical dislocation. The oesophagus was dissected from immediately proximal to the stomach (including piece of stomach to mark distal end) up to the level of the trachea and then placed in fresh Krebs' solution.

The outer skeletal muscle layer was removed in one go by peeling it away from the underlying smooth muscle layer using forceps (stomach to tracheal direction). The remaining inner tube of smooth muscle was known as the TMM. This was trimmed to 2 cm from the original 'stomach-end' and the rest discarded.

The TMMs were mounted as whole 'open' tubes in longitudinal orientation in 5ml organ baths filled with warm (32°C) aerated Krebs. Tissues were placed under an initial tension of 750mg and allowed to equilibrate for 60 minutes. The tissues were re-tensioned twice at 15 minute intervals during the equilibration period. The pump flow rate was set to 2ml / min during this time.

Following equilibration, the pump was switched off. The tissues were

exposed to 1 μ M carbachol and contracted and reached a steady contractile plateau within 15 minutes. Tissues were then subject to 1 μ M 5-HT (this was to prime the tissues). The tissues relaxed in response to 5-HT fairly rapidly - within 1 minute. As soon as maximal relaxation has occurred and a measurement taken, the tissues were washed at maximum rate (66ml/min) for at least 1 minute and until the original baseline (pre-carbachol and 5-HT) has returned (usually, the baseline drops below the original one following initial equilibration). The pump flow rate was reduced to 2ml/min and the tissues left for 60 minutes.

A cumulative concentration-effect-curve (CEC) to 5-HT was constructed across the range 0.1 nM to 1 μM, in half-log unit increments (*5-HT curve 1* for data analysis). Contact time between doses was 3 minutes or until plateau established. Tissues responded quicker as concentration of 5-HT in the bath increases. At the end of the curve, the tissues were washed (at maximum rate) as soon as possible to avoid desensitisation of receptors. Pump rate was reduced to 2ml/min and the tissues left for 60 minutes.

A second CEC was carried out - either to 5-HT (for time control tissues), another 5-HT_4 agonist (standard) or a test compound (*curve 2* for data analysis) . Contact time varied for other 5-HT_4 agonists and test compounds and was tailored according to the tissues' individual responses to each particular agent. In tissues exposed to a test compound, a high concentration (1μM) of a 5-HT_4 antagonist (SB 203,186: 1*H*-Indole-3-carboxylic acid, 2-(1-piperidinyl)ethyl ester, Tocris) was added to the bath following the last concentration of test compound. This was to see if any agonist-induced relaxation (if present) could be reversed. SB 203,186 reversed 5-HT induced relaxation, restoring the tissue's original degree of carbachol-induced tone.

Agonist activity of test compounds was confirmed by pre-incubating tissues with 100nM standard 5HT_4 antagonist such as SB 203,186. SB 203,186 was added to the bath 5 minutes before the addition of carbachol prior to *curve 2*. Tissues must be 'paired' for data analysis i.e. the test compound in the absence of SB 203,186 in one tissue was compared with the test compound in the presence of SB

203,186 in a separate tissue. It was not possible to carry out a *curve 3* i.e. 5-HT curve 1, followed by the test compound *curve 2* (- SB 203,186), followed by the test compound *curve 3* (+ SB 203,186).

Agonist-induced cAMP elevation in human 5-HT$_{4(d)}$ transfected HEK293 cells

Human 5-HT$_{4(d)}$ transfected HEK293 cells were established in-house. The cells were grown at 37°C and 5% CO_2 in DMEM supplemented with 10% FCS, 20 mM HEPES (pH 7.4), 200 μg/ml hygromycin B (Gibco), 100 units/ml penicillin and 100 μg/ml streptomycin.

The cells were grown to 60-80% confluence. On the previous day before treatment with compounds dialyzed FCS (Gibco) was substituted for normal and the cells were incubated overnight.

Compounds were prepared in 96-well plates (12.5 μl/well). The cells were harvested with PBS/1 mM EDTA, centrifuged and washed with PBS. At the beginning of the assay, cell pellet was resuspended in DMEM supplemented with 20 mM HEPES, 10 μM pargyline (Sigma) and 1 mM 3-isobutyl-1-methylxanthine (Sigma) at the concentration of 1.6 x 10^5 cells/ml and left for 15 minutes at room temperature. The reaction was initiated by addition of the cells into plates (12.5 μl/well). After incubation for 15 minutes at room temperature, 1% Triton X-100 was added to stop the reaction (25 μl/well) and the plates were left for 30 minutes at room temperature. Homogenous time-resolved fluorescence-based cAMP (Schering) detection was made according to the manufacturer's instruction. ARVOsx multilabel counter (Wallac) was used to measure HTRF (excitation 320 nm, emission 665 nm/620 nm, delay time 50 μs, window time 400 μs).

Data was analyzed based on the ratio of fluorescence intensity of each well at 620 nm and 665 nm followed by cAMP quantification using cAMP standard curve. Enhancement of cAMP production elicited by each compound was normalized to the amount of cAMP produced by 1000 nM serotonin (Sigma).

Human dofetilide binding

Human HERG transfected HEK293S cells were prepared and grown in-house. The collected cells were suspended in 50 mM Tris-HCl (pH 7.4 at 4°C) and

homogenized using a hand held Polytron PT 1200 disruptor set at full power for 20 sec on ice. The homogenates were centrifuged at 48,000 x g at 4 °C for 20 min. The pellets were then resuspended, homogenized, and centrifuged once more in the same manner. The final pellets were resuspended in an appropriate volume of 50 mM Tris-HCl, 10 mM KCl, 1 mM $MgCl_2$ (pH 7.4 at 4°C), homogenized, aliquoted and stored at -80°C until use. An aliquot of membrane fractions was used for protein concentration determination using BCA protein assay kit (PIERCE) and ARVOsx plate reader (Wallac).

Binding assays were conducted in a total volume of 200 µl in 96-well plates. Twenty µl of test compounds were incubated with 20 µl of [^{3}H]-dofetilide (Amersham, final 5 nM) and 160 µl of membrane homogenate (25 µg protein) for 60 minutes at room temperature. Nonspecific binding was determined by 10 µM dofetilide at the final concentration. Incubation was terminated by rapid vacuum filtration over 0.5% presoaked GF/B Betaplate filter using Skatron cell harvester with 50 mM Tris-HCl, 10 mM KCl, 1 mM $MgCl_2$, pH 7.4 at 4°C. The filters were dried, put into sample bags and filled with Betaplate Scint. Radioactivity bound to filter was counted with Wallac Betaplate counter.

I_{HERG} assay

HEK 293 cells which stably express the HERG potassium channel were used for electrophysiological study. The methodology for stable transfection of this channel in HEK cells can be found elsewhere (Z.Zhou et al., 1998, Biophysical journal, 74, pp230-241). Before the day of experimentation, the cells were harvested from culture flasks and plated onto glass coverslips in a standard MEM medium with 10% FCS. The plated cells were stored in an incubator at 37°C maintained in an atmosphere of 95%O_2/5%CO_2. Cells were studied between 15-28hrs after harvest.

HERG currents were studied using standard patch clamp techniques in the whole-cell mode. During the experiment the cells were superfused with a standard external solution of the following composition (mM); NaCl, 130; KCl, 4; $CaCl_2$, 2; $MgCl_2$, 1; Glucose, 10; HEPES, 5; pH 7.4 with NaOH. Whole-cell recordings was

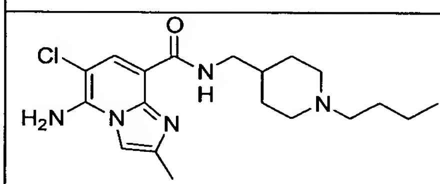
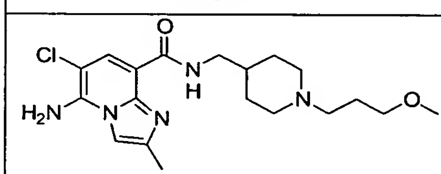
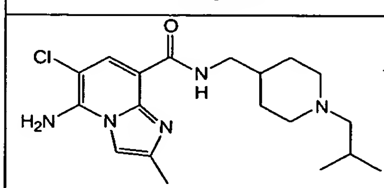
made using a patch clamp amplifier and patch pipettes which have a resistance of 1-3MOhm when filled with the standard internal solution of the following composition (mM); KCl, 130; MgATP, 5; $MgCl_2$, 1.0; HEPES, 10; EGTA 5, pH 7.2 with KOH. Only those cells with access resistances below 15MΩ and seal resistances >1GΩ was accepted for further experimentation. Series resistance compensation was applied up to a maximum of 80%. No leak subtraction was done. However, acceptable access resistance depended on the size of the recorded currents and the level of series resistance compensation that can safely be used. Following the achievement of whole cell configuration and sufficient for cell dialysis with pipette solution (>5min), a standard voltage protocol was applied to the cell to evoke membrane currents. The voltage protocol is as follows. The membrane was depolarized from a holding potential of -80mV to +20mV for 1000ms. This was followed by a descending voltage ramp (rate 0.5mV $msec^{-1}$) back to the holding potential. The voltage protocol was applied to a cell continuously throughout the experiment every 4 seconds (0.25Hz). The amplitude of the peak current elicited around –40mV during the ramp was measured. Once stable evoked current responses were obtained in the external solution, vehicle (0.5% DMSO in the standard external solution) was applied for 10-20 min by a peristaltic pump. Provided there were minimal changes in the amplitude of the evoked current response in the vehicle control condition, the test compound of either 0.3, 1, 3, 10μM was applied for a 10 min period. The 10 min period included the time which supplying solution was passing through the tube from solution reservoir to the recording chamber via the pump. Exposing time of cells to the compound solution was more than 5min after the drug concentration in the chamber well reached the attempting concentration. There reversibility. Finally, the cells was exposed to high dose of dofetilide (5μM), a specific IKr blocker, to evaluate the insensitive endogenous current.

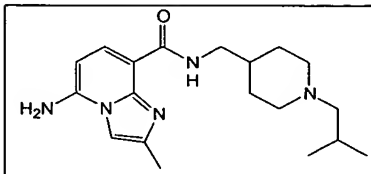
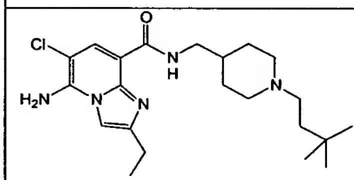
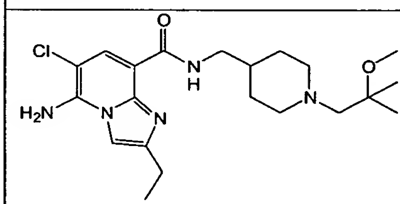
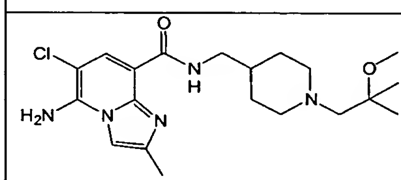
All experiments were performed at room temperature (23 ± 1°C). Evoked membrane currents were recorded on-line on a computer, filtered at 500-1KHz (Bessel -3dB) and sampled at 1-2KHz using the patch clamp amplifier and a specific

data analyzing software. Peak current amplitude, which occurred at around –40mV, was measured off line on the computer.

The arithmetic mean of the ten values of amplitude was calculated under control conditions and in the presence of drug. Percent decrease of I_N in each experiment was obtained by the normalized current value using the following formula: $\mathbf{I_N = (1- I_D/I_C)x100}$, where I_D is the mean current value in the presence of drug and I_C is the mean current value under control conditions. Separate experiments were performed for each drug concentration or time-matched control, and arithmetic mean in each experiment is defined as the result of the study.

Test result is summarized as follows:

Chemical Structure	**5HT4 Binding Ki [nM]**	**Dofetilide Binding Ki [μM]**	**TI (Defetilide/5HT4)**
 Compound A	1.2	2.3	1,900
 Compound B	4.6	6.0	1,300
 Compound of **Example 1** of this invention	0.82	5.75	7,000

 Compound of **Example 2** of this invention	3.1	24.1	7,800
 Compound of **Example 3** of this invention	0.77	3.87	5,000
 Compound of **Example 4** of this invention	1.2	22.3	19,000
 Compound of **Example 5** of this invention	2.0	> 24.0	> 12,000

(wherein **TI** is a value of { Dofetilide Binding Ki [μM]/ 5HT4 Binding Ki [nM]x1000})

The compounds of Example **1-5** showed a TI value in the range of 5,000 – 19,000, whereas a structurally similar comparative compound **A** and **B** showed TI values of 1,900 and 1,300.

The imidazopyridine compounds of this invention can be administered via either the oral, parenteral or topical routes to mammals. In general, these compounds are most desirably administered to humans in doses ranging from about

0.3 mg to about 750 mg per day, preferably from about 10 mg to about 500 mg per day, although variations will necessarily occur depending upon the weight and condition of the subject being treated, the disease state being treated and the particular route of administration chosen. However, for example, a dosage level that is in the range of from about 0.06 mg to about 2 mg per kg of body weight per day is most desirably employed for treatment of inflammation.

The compounds of the present invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by either of the above routes previously indicated, and such administration can be carried out in single or multiple doses. More particularly, the novel therapeutic agents of the invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various nontoxic organic solvents, etc. Moreover, oralpharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutically-effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5% to about 70% by weight, preferably about 10% to about 50% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dipotassium phosphate and glycine may be employed along with various disintegrants such as starch and preferably corn, potato or tapioca starch, alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs

are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of a compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH>8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intra-articular, intra-muscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. Additionally, it is also possible to administer the compounds of the present invention topically when treating inflammatory conditions of the skin and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

Examples

The invention is illustrated in the following non-limiting examples in which, unless stated otherwise: all operations were carried out at room or ambient temperature, that is, in the range of about 18-25 °C; evaporation of solvent was carried out using a rotary evaporator under reduced pressure with a bath temperature of up to about 60 °C; reactions were monitored by thin layer chromatography (tlc) and reaction times are given for illustration only; melting points (m.p.) given are uncorrected (polymorphism may result in different melting points); the structure and purity of all isolated compounds were assured by at least one of the following techniques: tlc (Merck silica gel 60 F_{254} precoated TLC plates or Merck NH_2 F_{254s} precoated HPTLC plates), mass spectrometry, nuclear magnetic resonance (NMR), infrared red absorption spectra (IR) or microanalysis. Yields are given for illustrative purposes only. Flash column chromatography was carried out using Merck silica gel 60 (230-400 mesh ASTM) or Fuji Silysia Chromatorex® DU3050

(Amino Type, 30~50 μm). Low-resolution mass spectral data (EI) were obtained on a Automass 120 (JEOL) mass spectrometer. Low-resolution mass spectral data (ESI) were obtained on a Quattro II (Micromass) mass spectrometer. NMR data was determined at 270 MHz (JEOL JNM-LA 270 spectrometer) or 300 MHz (JEOL JNM-LA300) using deuterated chloroform (99.8% D) or dimethylsulfoxide (99.9% D) as solvent unless indicated otherwise, relative to tetramethylsilane (TMS) as internal standard in parts per million (ppm); conventional abbreviations used are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad, etc. IR spectra were measured by a Shimazu infrared spectrometer (IR-470). Optical rotations were measured using a JASCO DIP-370 Digital Polarimeter (Japan Spectroscopic CO, Ltd.). Chemical symbols have their usual meanings; b.p. (boiling point), m.p. (melting point), l (liter(s)), ml (milliliter(s)), g (gram(s)), mg (milligram(s)), mol (moles), mmol (millimoles), eq. (equivalent(s)).

EXAMPLE 1: 5-AMINO-6-CHLORO-*N*-[(1-ISOBUTYLPIPERIDIN-4-YL)METHYL]-2-METHYLIMIDAZO[1,2-*a*]PYRIDINE-8-CARBOXAMIDE

Step 1. methyl 2,6-bis[(2,2-dimethylpropanoyl)amino]nicotinate

In a 5 L, 4-necked round bottom flask, immersed in ice-cold ethanol-isopropanol (isopropanol 13%, -15°C) bath, to a solution of 2,6-bis[(2,2-dimethylpropanoyl)amino]pyridine (*J. Am. Chem. Soc.* **1986**, *108*, 3310-3318, 126 g, 454 mmol) in anhydrous tetrahydrofuran (1.5 L) was added 2.66 M solution of *n*-buthyllithium in hexane (598 mL) dropwise from a dropping funnel (1 L) during the period of 6 h under nitrogen atmosphere (internal temperature was maintained at -15°C ~ -5°C). The resulting solution was stirred at 0°C (internal temperature) for 12 h under nitrogen atmosphere. The formation of yellowish precipitate was noticed. Then the suspension was cooled to -15°C, dimethyl carbonate (194 mL, 2.3 mmol) was added in one portion. The reaction solution was stirred at 0°C for 1 h, quenched with 1. 5 L of 1 N aqueous hydrochloric acid, pH value was controlled to ~4.5 by adding 1 N aqueous hydrochloric acid, then 600 mL of ethyl acetate was added. After the layers were separated, the organic layer was washed with 1 L of 0.2 N aqueous NaOH (1 L) and brine (500 mL). Each aqueous layer was extracted

with ethyl acetate (300 mL) twice. Combined organic layer was dried over sodium sulfate (~300 g) and concentrated. The residue was diluted with diisopropylether (300 mL) and the solution was evaoprated to remove the residual ethyl acetate azeotropically. The residue was dissolved with diisopropylether (360 mL) at 60°C with gentle stirring, and then the small portion of the crystalline of the desired product (~5 mg) was added as seed. The formation of a pale yellow precipitate was noticed. The resulting suspension was cooled to room temperature (during the period of 2 h), and stirred at room temperature for 2 h. The suspension was filtered through paper filter, then the cake was washed with diisopropylether (80 mL). The solid was dried under reduced pressure at room temperature for 1 day to give the title compound (120 g, 358 mmol, 79%) as a pale yellow solid.

MS (EI) m/z: 335 (M^+)

^{1}H-NMR ($CDCl_3$) δ: 1.32 (9 H, s), 1.35 (9 H, s), 3.93 (3 H, s), 8.04 (1 H, d, J=8.8 Hz), 8.31 (1 H, d, J=8.8 Hz), 9.32 (1 H, br s), 11.47 (1 H, br s).

<u>Step 2. methyl 5-chloro-2,6-bis[(2,2-dimethylpropanoyl)amino]nicotinate</u>

To a solution of methyl 2,6-bis[(2,2-dimethylpropanoyl)amino]nicotinate (EXAMPLE 1, Step 1, 186 g, 555 mmol) in anhydrous *N,N*-dimethylformamide (930 mL) was added a solution of *N*-chlorosuccinimide (81.5 g, 610 mmol) in anhydrous *N,N*-dimethylformamide (560 mL) dropwise from a dropping funnel (1 L) during the period of 2.5 h at 70°C (internal temperature) under nitrogen atmosphere. The resulting pale yellow solution was stirred at 70°C for 2 h and allowed to cool to room temperature. The reaction solution was quenched with a solution of 250 g of ammonium chloride and 100 g of sodium hydrogen sulfite in 3 L of water and extracted with a mixture of ethyl acetate and hexane (3 L, 3:1). After the layers were separated, the organic layer was washed with water (2 L), dried over sodium sulfite (300 g) and evaporated. The residual pale yellow solid was added isopropylether (1.4 L) and the resulting mixture was stirred at 60°C for 2 h. After the mixture was cooled to room temperature, the mixture was filtered through paper filter, and the cake was washed with isopropylether (200 mL), dried under

reduced pressure at room temperature to give (153.9 g, 416 mmol) of the title compound as a white solid.

MS (ESI+) m/z: 370 (M+1)

^{1}H-NMR ($CDCl_3$) δ: 1.34 (18 H, s), 3.94 (3 H, s), 8.30 (1 H, s), 8.51 (1 H, br s), 11.12 (1 H, br s).

Step 3. methyl 2,6-diamino-5-chloronicotinate

To a colorless solution of methyl 5-chloro-2,6-bis[(2,2-dimethylpropanoyl)amino]-nicotinate (EXAMPLE 1, Step 2, 153.9 g, 416 mmol) in methanol (1.5 L) was added a solution of potassium *tert*-butoxide (185 g, 1.65 mol) in methanol (500 mL) dropwise during the period of 20 min at room temperature under nitrogen atmosphere. Dissolving potassium *tert*-butoxide in methanol was exothermic, so potassium *tert*-butoxide must be added portionwise from powder addition funnel to methanol during the period of 2 h with ice-cold water bath. After the addition was completed, the reaction solution was stirred at reflux temperature for 1 h under nitrogen atmosphere, and cooled to room temperature. The resulting suspension was evaporated and ca. 1.3 L of methanol was removed (ca. 700 mL of methanol was remained). To this mixture was added water (1.2 L) and stirred at room temperature for 1 h with water bath (internal temperature was maintained at 20°C), then the resulting suspension was filtered through paper filter and the pale yellow solid was dried under reduced pressure at 50 °C for 12 h to give 74.3 g (368.9 mmol, 89%) of the title compound as a pale yellow crystal.

Rf value: 0.28 (ethyl acetate/hexane=1 : 2).

^{1}H-NMR (DMSO-d_6) δ: 3.71 (3 H, s), 6.77 (2 H, br s), 6.94 (2 H, br s), 7.72 (1 H, s).

Step 4. methyl 5-amino-6-chloro-2-methylimidazo[1,2-*a*]pyridine-8-carboxylate

A mixture of methyl 2,6-diamino-5-chloronicotinate (EXAMPLE 1, Step 3, 15 g, 74.4 mmol), bromoacetone (10.4 mL, 112 mmol) and sodium iodide (16.7 g, 112 mmol) in methanol (700 mL) was stirred under reflux for 22 h. Another 2.5 mL (33 mmol) of bromoacetone was added and the stirring was continued for 24 h.

The reaction mixture was quenched with saturated aqueous sodium carbonate and removed methanol *in vacuo*. The residue was extracted with ethyl acetate (250 mL x 10) adding a small amount of methanol to dissolve the organic solid. The organic extracts were dried over sodium sulfate and concentrated. Purification by column chromatography on silica gel eluting with dichloromethane/methanol (20: 1) gave a dark brown solid, which was washed with ethyl acetate and filtered to afford 10.5 g (43.9 mmol, 59%) of the title compound as a pale brown solid.
MS (FAB) m/z: 240 (M+1).
^{1}H-NMR (DMSO-d_6) δ: 2.34 (3 H, s), 3.80 (3 H, s), 7.70 (2 H, br s), 7.83 (1 H, s), 7.85 (1H, s).

<u>Step 5. methyl 5-amino-6-chloro-2-methylimidazo[1,2-*a*]pyridine-8-carboxylic acid</u>
A mixture of methyl 5-amino-6-chloro-2-methylimidazo[1,2-*a*]pyridine-8-carboxylate (EXAMPLE 1, Step 4, 10.5 g, 43.9 mmol,) and 1 N lithium hydroxide (87.7 mL, 87.7 mmol) in methanol (100 mL) was stirred under reflux for 1 h. After removal of the solvent *in vacuo*, the residue was suspended with water and treated with 2 N hydrochloric acid to adjust to pH 4. The resulting solid was filtered, washed with water and diethyl ether and dried *in vacuo* with heating to give 9.5 g (42.2 mmol, 96%) of the title compound as a brown solid.
MS (EI) m/z: 225 (M^+).
^{1}H-NMR (DMSO-d_6) δ: 2.38 (3 H, s), 7.88 (1 H, s), 7.92 (1 H, s), 8.00 (2 H, br s). A signal due to COOH was not observed.

<u>Step 6. 5-amino-6-chloro-*N*-[(1-isobutylpiperidin-4-yl)methyl]- 2-methylimidazo[1,2-*a*]pyridine-8-carboxamide</u>
To a suspension of 5-amino-6-chloro-2-methylimidazo[1,2-*a*]pyridine-8-carboxylic acid (EXAMPLE 1, Step 5, 7.0 g, 31.0 mmol) in *N,N*-dimethylformamide (140 mL) was added 1,1'-carbonyldiimidazole (6.0g, 37.2 mmol) at room temperature. After stirring for 5 min, the temperature was raised to 60°C and the stirring was continued for 2.5 h. Another 2.5 g (15.5 mmol) of 1,1'-carbonyldiimidazole was added at

room temperature and the mixture was stirred at the temperature for 40 min and at 60°C for 2 h. Then a *N,N*-dimethylformamide (25 mL) solution of (1-isobutylpiperidin-4-yl)methylamine (*Bioorg. Med. Chem.* **1999**, *7*, 2271-2281, 6.3 g, 37.2 mmol) was added at room temperature and the stirring was continued for 18 h. The mixture was quenched with water (165 mL). The resulting precipitate was collected by filtration and washed with water (200 mL). The filtrate was extracted with ethyl acetate (150 mL x 2). The precipitate and the organic extracts were combined and concentrated. The residue was purified by column chromatography (basic silica gel) eluting with ethyl acetate/hexane (1:1 to 2:1) to give a pale yellow solid (8.39 g), which was washed with diethyl ether (200 mL) to give 7.3 g (19.4 mmol, 63 %) of the title compound as a white solid.

MS (EI) m/z: 377(M^+).

m.p.: 216-219°C.

IR (KBr) ν: 3472, 3246, 2951, 2920, 1638, 1607, 1562, 1545, 1437, 1321, 1265, 1148, 1101, 710 cm^{-1}.

^{1}H-NMR (DMSO-d_6) δ: 0.82 (6 H, d, J=6.6 Hz), 1.18-1.31 (2 H, m), 1.41-1.55 (1 H, m), 1.61-1.83 (5 H, m), 1.97 (2 H, d, J=7.2 Hz), 2.37 (3 H, s), 2.78-2.81 (2 H, m), 3.28 (2 H, t, J=6.0 Hz), 7.58 (2 H, br s), 7.86 (1 H, s), 7.88 (1 H, s), 9.92 (1 H, br).

Anal. Calcd. for $C_{19}H_{28}ClN_5O$: C, 60.39; H, 7.47; N, 18.53. Found: C, 60.33; H, 7.68; N, 18.43.

EXAMPLE 2: 5-AMINO-*N*-[(1-ISOBUTYLPIPERIDI-4-YL)METHYL]-2-METHYLIMIDAZO[1,2-*a*]PYRIDINE-8-CARBOXAMIDE

A mixture of 5-amino-6-chloro-*N*-[(1-isobutylpiperidin-4-yl)methyl]- 2-methylimidazo[1,2-*a*]pyridine-8-carboxamide (EXAMPLE 1, Step 6, 134 mg, 0.36 mmol), 10% palladium charcoal (67 mg) and ammonium formate (224 mg, 3.6 mmol) in methanol (5 mL) was stirred at room temperature for 4 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was treated with 25% aqueous ammonia (10 mL), extracted with dichloromethane

(20 mL x 2) and washed with brine (20 mL). Removal of the solvent gave 92.4 mg (0.37 mmol, 76%) of the title compound as a yellow amorphous powder.

MS (EI) m/z: 343(M^+).

IR (KBr) ν: 3327, 3180, 2953, 2924, 1638, 1558, 1516, 1431, 1290 cm^{-1}.

^{1}H-NMR (DMSO-d_6) δ: 0.83 (6 H, d, J=6.5 Hz), 1.17-1.32 (2 H, m), 1.40-1.54 (1 H, m), 1.61-1.85 (5 H, m), 1.99 (2 H, d, J=7.3 Hz), 2.36 (3 H, s), 2.79-2.83 (2 H, m), 3.25-3.29 (2 H, m), 6.04 (1 H, d, J=8.1 Hz), 7.26 (2 H, br s), 7.68 (1 H, s), 7.85 (1 H, d, J=8.1 Hz), 10.00 (1 H, br).

Anal. Calcd. for $C_{19}H_{29}N_5O{\cdot}0.05C_4H_8O_2{\cdot}0.5H_2O$: C, 64.62; H, 8.59; N, 19.62. Found: C, 64.89; H, 8.64; N, 19.36.

EXAMPLE 3: 5-AMINO-6-CHLORO-*N*-{[1-(3,3-DIMETHYLBUTYL)PIPERIDIN-4-YL]METHYL}-2-ETHYLIMIDAZO[1,2-*a*]PYRIDINE-8-CARBOXAMIDE

<u>Step1, methyl 5-amino-6-chloro-2-ethylimidazo[1,2-*a*]pyridine-8-carboxylate</u>

The title compound was prepared according to the procedure described in the step 4 in EXAMPLE 1 from methyl 2,6-diamino-5-chloro-3-pyridinecarboxylate (EXAMPLE 1, Step 3) and 1-bromo-2-butanone.

MS (EI) m/z: 253 (M^+).

^{1}H-NMR (DMSO-d_6) δ: 1.27 (3 H, t, J=7.5 Hz), 2.72 (2 H, q, J=7.5 Hz), 3.80 (3 H, s), 7.72 (2 H, s), 7.86 (1 H, s), 7.87 (1 H, s).

<u>Step 2, 5-amino-6-chloro-2-ethylimidazo[1,2-*a*]pyridine-8-carboxylic acid</u>

The title compound was prepared according to the procedure described in the step 5 in EXAMPLE 1, from methyl 5-amino-6-chloro-2-ethylimidazo[1,2-*a*]pyridine-8-carboxylate (EXAMPLE 3, Step 1).

MS (EI) m/z: 239 (M^+).

^{1}H-NMR (DMSO-d_6) δ: 1.27 (3 H, t, J=7.2 Hz), 2.74 (2 H, q, J=7.2 Hz), 7.88 (1 H, s), 7.95 (1 H, s). A signal due to COOH was not observed.

Step 3. *tert*-butyl 4-({[(5-amino-6-chloro-2-ethylimidazo[1,2-*a*]pyridin-8-yl)carbonyl] amino}methyl)piperidine-1-carboxylate

A mixture of 5-amino-6-chloro-2-ethylimidazo[1,2-*a*]pyridine-8-carboxylic acid (EXAMPLE 3, Step 2, 10.00 g, 41.72 mmol), *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate (J. Prugh, L. A. Birchenough and M. S. Egbertson, *Synth. Commun.*, **1992**, *22*, 2357-60, 15.20 g, 70.93 mmol), DEPC (10.76 mL, 70.93 mmol) and diisopropylethylamine (18.17 mL, 104.4 mmol) in *N,N*-dimethylformamide (267 mL) was stirred at room temperature for 43 h. The solvent was removed by evaporation. The residue was basified with aqueous sodium bicarbonate (40 mL), and extracted with dichloromethane (5 x 100 mL). The combined extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue eluting with dichloromethane/methanol (100:1 to 20:1) afforded 19.08 g (90%) of the title compound as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.35 (3 H, t, J=7.6 Hz), 1.45 (9 H, s), 1.88-1.28 (5 H, m), 2.88-2.64 (2 H, m), 3.52-3.38 (2 H, m), 4.30-3.97 (4 H, m), 5.17 (2 H, br s), 7.21 (1 H, s), 8.19 (1 H, s), 10.21 (1 H, bv).

Step 4. 5-amino-6-chloro-2-ethyl-*N*-(piperidin-4-ylmethyl)imidazo[1,2-*a*]pyridine-8-carboxamide

To a stirred solution of *tert*-butyl 4-({[(5-amino-6-chloro-2-ethylimidazo[1,2-*a*]-pyridin-8-yl)carbonyl]amino}methyl)piperidine-1-carboxylate (EXAMPLE 3, Step 3, 13.71 g, 31.44 mmol) in 10% hydrochloric acid methanol solution (314 mL) was added concentrated hydrochloric acid (10 mL). After stirring at room temperature for 26 h, the mixture was concentrated to about 50 mL *in vacuo*. The residue was basified with an excess of sodium carbonate and then insoluble material was filtered off. The filtrate was concentrated azeotropically with ethanol and diluted with a mixture of dichloromethane and methanol (5:1, 200 mL). The formed inorganic solid was filtered off again. The filtrate was concentrated *in vacuo* to give a pale yellow amorphous, which was crystallized from ethanol to afford 4.79 g (45%) of the title compound as an off-white solid. Furthermore, 5.09 g (48%) of the

compound was obtained from the mother liquid.

MS (ESI) m/z: 336.17 $(M+H)^+$, 334.14 $(M-H)^-$.

m.p. (TG/DTA): 153°C.

IR (KBr) ν: 3387, 3300, 3188, 2964, 1639, 1605, 1562, 1514 cm^{-1}.

^{1}H-NMR (DMSO-d_6) δ: 1.30-0.90 (2 H, m), 1.30 (3 H, t, J=7.6 Hz), 1.74-1.50 (3 H, m), 2.55-2.36 (2 H, m), 2.75 (2 H, q, J=7.6 Hz), 3.04-2.86 (2 H, m), 3.27 (2 H, t, J=5.9 Hz), 7.86 (1 H, s), 7.94 (1 H, s), 10.05-9.94 (1 H, m).

Anal. Calcd. for $C_{16}H_{22}ClN_5O{\bullet}2.5H_2O{\bullet}0.8EtOH$: C, 50.70; H, 7.49; N, 16.80. Found: C, 50.57; H, 7.27; N, 16.80.

Step 5. 5-amino-6-chloro-*N*-{[1-(3,3-dimethylbutyl)piperidin-4-yl]methyl}-2-ethylimidazo[1,2-*a*]pyridine-8-carboxamide

To a stirred mixture of 5-amino-6-chloro-2-ethyl-*N*-(piperidin-4-ylmethyl)imidazo [1,2-*a*]pyridine-8-carboxamide (EXAMPLE 3, Step 4, 450 mg, 1.34 mmol) and 1-bromo-3,3-dimethylbutane (606 mg, 3.35 mmol) in *N,N*-dimethylformamide (6 mL) were added potassium carbonate (648 mg, 4.69 mmol) and sodium iodide (502 mg, 3.35 mmol). After stirring at 90°C for 42 h, the reaction mixture was cooled and evaporated. The residue was diluted with dichloromethane (30 mL) and water (20 mL). The mixture was extracted with dichloromethane (2 x 30 mL). The combined extract was washed with brine, dried over magnesium sulfate, and concentrated. Flash chromatography (NH-silica gel) of the residue eluting with hexane/ethyl acetate (1:1 to 1:2) afforded a brown solid (296 mg), which was recrystallized from ethyl acetate to give 191 mg (34%) of the title compound as a pale brown solid.

MS (ESI) m/z: 420 $(M+H)^+$, 418 $(M-H)^-$.

m.p. (TG/DTA): 234°C.

IR (KBr) ν: 3136, 2947, 1636, 1607, 1558 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ: 0.89 (9 H, s), 1.36 (3 H, t, J=7.5 Hz), 1.98-1.36 (9 H, m), 2.37-2.26 (2 H, m), 2.83 (2 H, q, J=7.5 Hz), 3.02-2.92 (2 H, m), 3.45 (2 H, t, J=6.2 Hz), 4.96 (2 H, bsv), 7.12 (1 H, s), 8.20 (1 H, s), 10.17 (1 H, bs).

Anal. Calcd. for $C_{22}H_{34}ClN_5O$: C, 62.91; H, 8.16; N, 16.68. Found: C, 62.71; H, 8.20; N, 16.62.

EXAMPLE 4: 5-AMINO-6-CHLORO-2-ETHYL-*N*-{[1-(2-METHOXY-2-METHYLPROPYL)PIPERIDIN-4-YL]METHYL}IMIDAZO[1,2-*a*]PYRIDINE-8-CARBOXAMIDE

Step 1, *tert*-butyl 4-[(dibenzylamino)carbonyl]piperidine-1-carboxylate

To a stirred mixture of 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (*J. Med. Chem.* **1998**, *41*, 2492-2502, 3.0 g, 13.1 mmol), dibenzylamine (2.5 mL, 13.1 mmol) and diisopropylethylamine (3.4 mL, 19.7 mmol) in dichrolomethane (150 mL) was added PyBroP (bromo-tris-pyrrolidino-phosophonium hexafluorophosphate) (6.1 g, 15.7 mmol) was added at 0°C. The mixture was stirred at ambient temperature for 18h and partitioned between dichloromethane and water. After extraction with dichloromethane, the combined organic phase was dried over magnesium sulfate and concentrated. The residue was purified by flash column chromatography on silica gel eluting with hexane/ethyl acetate (6:1) to afford 4.0 g (75%) of the title compound as a colorless amorphous powder.

^{1}H-NMR ($CDCl_3$) δ: 1.43 (9 H, s), 1.50-1.74 (4 H, m), 1.78-1.95 (2 H, m), 2.58-2.75 (2 H, m), 4.45-4.51 (1 H, m), 7.11-7.44 (10 H, m).

Step 2. *N,N*-dibenzylpiperidine-4-carboxamide

To a stirred solution of *tert*-butyl 4-[(dibenzylamino)carbonyl]piperidine-1-carboxylate (EXAMPLE 4, Step 1, 4.0 g, 10.0 mmol) in methanol (550 mL) was added 4N HCl dioxane solution (80 mL, 320 mmol) at 0°C. The mixture was stirred for 6h and evaporated. The resulting amorphous was dissolved in aqueous ammonia and the mixture was extracted with dichloromethane. The combined extract was dried over magnesium sulfate, and concentrated to afford 3.0 g (99%) of the title compound as a colorless amorphous powder.

MS (ESI) m/z: 309 $(M+H)^+$, 307 $(M-H)^-$.

Step 3. *N,N*-dibenzyl-*N*-(piperidin-4-ylmethyl)amine

To a suspension of lithium aluminum hydride (min.80%, 1.50 g, 40.0 mmol) in tetrahydrofuran (50 ml) was added dropwise a solution of *N,N*-dibenzylpiperidine-4-carboxamide (EXAMPLE 4, Step 2, 3.08 g, 10.0 mmol) in tetrahydrofuran (50 ml) at 0°C over 15 min. The mixture was stirred at 0°C for 30 min and at 40°C for 4 h. After cooling to 0°C, water (3.3 ml), 15% NaOH aqueous solution (3.3 ml), and then water (10 ml) were carefully added dropwise. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo* to give 2.85 g (97%) of the title compound as a pale yellow oil.

MS (ESI) m/z: 295 $(M+H)^+$, 293 $(M-H)^-$.

^{1}H-NMR ($CDCl_3$) δ: 0.90-1.10 (2 H, m), 1.70-1.92 (4 H, m), 2.20 (2 H, d, J=7.2 Hz), 2.78 (1 H, s), 2.86 (2 H, d, J=11.5 Hz), 3.48 (4 H, s), 7.16-7.35 (10 H, m).

Step 4. 1-{4-[(dibenzylamino)methyl]piperidin-1-yl}-2-methylpropan-2-ol

A mixture of *N,N*-dibenzyl-*N*-(piperidin-4-ylmethyl)amine (EXAMPLE 4, Step 3, 3.3g, 11.21 mmol) and 2,2-dimethyloxirane (12.1 mL, 134.5 mmol) in methanol (40 mL) and tetrahydrofuran (5 mL) was heated at 40°C with stirring for 17h. The volatile components were removed and the residue was purified by flash column chromatography on amine gel eluting with hexane/ethyl acetate (50:1) to afford 3.0 g (73%) of the title compound as a colorless amorphous.

MS (ESI) m/z: 367 $(M+H)^+$.

Step 5. *N,N*-dibenzyl-*N*-{[1-(2-methoxy-2-methylpropyl)piperidin-4-yl]methyl}amine

To a suspension of sodium hydride (abt. 60% in mineral oil, 342 mg, 8.6 mmol) in a mixture of tetrahydrofuran (20 mL) and *N,N*-dimethylformamide (10 mL) was added a solution of 1-{4-[(dibenzylamino)methyl]piperidin-1-yl}-2-methylpropan-2-ol (EXAMPLE 4, Step 4, 3.0 g, 8.2 mmol) in tetrahydrofuran (20 ml) at 0°C. Afer being stirred at the same temperature for 30 min, 0.53 mL (8.6 mmol) of iodomethane was added to the mixture. The mixture was stirred at ambient

temperature for 3 days. The mixture was partitioned between ethyl acetate and water. After extraction with ethyl acetate, the combined organic phase was dried over magnesium sulfate, and concentrated. The residue was purified by flash column chromatography on amine gel eluting with hexane/ethyl acetate (100:1) to afford 0.76 g (24%) of the title compound as colorless amorphous.

MS (ESI) m/z: 381 $(M+H)^+$.

^{1}H-NMR ($CDCl_3$) δ: 1.12 (6 H, s), 0.99-1.19 (2 H, m), 1.43-1.60 (1 H, m), 1.69-1.74 (2 H, m), 2.01-2.11 (2 H, m), 2.11-2.26 (4 H, m), 2.84-2.91 (2 H, m), 3.18 (3 H, s), 3.50 (3 H, s), 7.18-7.37 (10 H, m).

Step 6. [1-(2-methoxy-2-methylpropyl)piperidin-4-yl]methylamine

To a solution of *N,N*-dibenzyl-*N*-{[1-(2-methoxy-2-methylpropyl)piperidin-4-yl]methyl}amine (EXAMPLE 4, Step 5, 756mg, 1.85 mmol) and ammonium formate (583 mg, 9.24 mmol) in methanol (40 mL) and water (15 mL) was added 10% palladium on carbon (185mg) at ambient temperature. The mixture was heated at 80°C for 6h. After cooling, the mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo*. The obtained residue was partitioned between dichlorometane and aqueous ammonia. After extraction with dichloromethane, the combined organic extract was dried over magnesium sulfate and concentrated to give 275 mg (66%) of the title compound as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.15 (6 H, s), 1.17-1.26 (2 H, m), 1.58-1.68 (1 H, m), 2.05-2.19 (2 H, m), 2.28 (2 H, s), 2.53-2.56 (2 H, m), 2.90-2.98 (2 H, m), 3.20 (3 H, s).

Step 7. 5-amino-6-chloro-2-ethyl-*N*-{[1-(2-methoxy-2-methylpropyl)piperidin-4-yl]methyl}imidazo[1,2-*a*]pyridine-8-carboxamide

The title compound was prepared according to the procedure described in the step 6 in EXAMPLE 1, using 5-amino-6-chloro-2-ethylimidazo[1,2-*a*]pyridine-8-carboxylic acid (EXAMPLE 3, Step 2) and [1-(2-methoxy-2-methylpropyl)piperidin-4-yl]methylamine (EXAMPLE 4, Step 6).

MS (ESI) m/z: 422 $(M+H)^+$, 420$(M-H)^-$.

m.p.: 211°C.

IR (KBr) ν: 3466, 3250, 2955, 2930, 2918, 1632, 1620, 1600, 1545, 1437, 1319, 1268, 1146, 1105, 998 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ: 1.16 (6 H, s), 1.35 (3 H, t, J=7.5 Hz), 1.71-1.76 (2 H, m), 2.29 (2 H, s), 2.82 (2 H, q, J=7.5 Hz), 2.46 (3 H, s), 2.93-2.97 (2 H, m), 3.43 (2 H, t, J=6.4 Hz), 4.97 (2 H, brs), 7.14 (1 H, s), 8.19 (1 H, s), 10.08 (1 H, br).

Anal. Calcd. for $C_{21}H_{32}ClN_5O_2 \cdot 0.5H_2O$: C, 59.14; H, 7.68; N, 16.42. Found: C, 59.03; H, 7.62; N, 16.24.

EXAMPLE 5: 5-AMINO-6-CHLORO-2-METHYL-*N*-{[1-(2-METHOXY-2-METHYLPROPYL)PIPERIDIN-4-YL]METHYL}IMIDAZO[1,2-*a*]PYRIDINE-8-CARBOXAMIDE

The title compound was prepared according to the procedure described in the step 6 in EXAMPLE 1 from 5-amino-6-chloro-2-methylimidazo[1,2-*a*]pyridine-8-carboxylic acid (EXAMPLE 1, Step 5) and [1-(2-methoxy-2-methylpropyl)piperidin-4-yl]methylamine (EXAMPLE 4, Step 6).

MS (ESI) m/z: 408 $(M+H)^+$, 406 $(M-H)^-$.

m.p.: 211°C.

IR (KBr) ν: 3470, 3342, 3208, 2940, 2918, 1655, 1601, 1555, 1545, 1437, 1319, 1288, 1266, 1147cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ: 1.16 (6 H, s), 1.39-1.47 (2 H, m), 1.71-1.76 (2 H, m), 2.16 (2 H, t, J=11.0 Hz), 2.29 (2 H, s), 2.46 (3 H, s), 2.93-2.97 (2 H, m), 3.20 (3 H, s), 3.43 (2 H, t, J=6.4 Hz), 4.97 (2 H, br s), 7.14 (1 H, s), 8.19 (1 H, s), 10.08 (1 H, br s).

Anal. Calcd. for $C_{21}H_{32}ClN_5O_2$: C, 58.89; H, 7.41; N, 17.17. Found: C, 58.62; H, 7.38; N, 16.93.

EXAMPLE 6: 5-AMINO-6-CHLORO-*N*-{[1-(2,2-DIMETHYLPROPYL)PIPERIDIN-4-YL]METHYL}-2-ETHYLIMIDAZO[1,2-*a*]PYRIDINE-8-CARBOXYAMIDE

Step 1. 1-(2,2-dimethylpropyl)piperidine-4-carboxyamide

To a solution of isonipecotamide (2 g, 15.6 mmol) and pivalaldehyde (2.0 mL, 18.7 mmol) in tetrahydrofuran (200 mL) was added titanium(IV) isopropoxide (4.6 mL, 15.6 mmol) and the mixture was stirred at room temperature for 21 h under nitrogen. Solvent was removed, the residue was dissolved in ethanol (60 mL) and sodium cyanoborohydride (1.6 g, 23.4 mmol) was added at room temperature. After stirring for 89 h, water (30 mL) was added, obtained precipitate was removed by filtration and the filtrate was concentrated. The residue was treated with water (30 mL) basified with 2 N sodium hydroxide, extracted with dichloromethane (30 mL x 3) and washed with brine (30 mL). The organic extracts were dried over sodium sulfate and concentrated to give a white solid, which was purified by flash column chromatography on silica gel eluting with dichloromethane/methanol/25% ammonia solution (20 : 1 : 0.1) to affoad 715 mg (23%) of the title compound as a white solid.

MS (ESI) m/z: 199 $(M+1)^+$.

^{1}H-NMR ($CDCl_3$) δ: 0.82 (9 H, s), 1.52-1.60 (4 H, m), 1.91-2.01 (3 H, m), 2.09-2.18 (2 H, m), 2.72-2.76 (2 H, m), 6.70 (1 H, br s), 7.24 (1 H, br s).

Step 2. {[1-(2,2-dimethylpropyl)piperidin-4-yl]methyl}amine

To a suspension of lithium aluminum hydride (342 mg, 7.2 mmol) in tetrahydrofuran (15 mL) was added a tetrahydrofuran solution (15 mL) of 1-(2,2-dimethylpropyl)piperidine-4-carboxyamide (EXAMPLE 6, Step 1, 715 mg, 3.6 mmol) at 0°C. The mixture was stirred at 40°C for 2 h, cooled to room temperature and quenched with sodium sulfate decahydrate and potassium fluoride. Filtration through a pad of Celite and concentration of the filtrate gave a crude of the title compound (785 mg) as a colorless oil.

MS (ESI) m/z: 185 $(M+1)^+$.

^{1}H-NMR ($CDCl_3$) δ: 0.85 (9 H, s), 1.11-1.28 (2 H, m), 1.49-1.86 (5 H, m), 2.12-2.19 (2 H, m), 2.54-2.56 (2 H, m), 2.78-2.81 (2 H, m), 3.67-3.69 (2 H, m).

Step 3. 5-amino-6-chloro-*N*-{[1-(2,2-dimethylpropyl)piperidin-4-yl]methyl}-2-ethylimidazo[1,2-*a*]pyridine-8-carboxyamide

The title compound was prepared according to the procedure described in the Step 6 in EXAMPLE 1, from 5-amino-6-chloro-2-ethylimidazo[1,2-a]pyridine-8-carboxylic acid (EXAMPLE 3, Step 2) and {[1-(2,2-dimethylpropyl)piperidin-4-yl]methyl}amine (EXAMPLE 6, Step 2).

MS (ESI) m/z: 406 $(M+1)^+$.

m.p. (TG/DTA): 252°C.

IR (KBr) ν: 3470, 3142, 3086, 2949, 1636, 1605, 1578, 1560, 1543, 1516, 1466, 1358, 1339, 1271, 1229 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ: 0.85 (9 H, s), 1.36 (3 H, t, J=7.5 Hz), 1.37-1.49 (2 H, m), 1.52-1.66 (1 H, m), 1.71-1.75 (2 H, m), 2.02 (2 H, s), 2.16-2.24 (2 H, m), 2.80-2.87 (4 H, m), 3.41-3.45 (2 H, m), 5.00 (2 H, br s), 7.16 (1 H, s), 8.20 (1 H, s), 10.17 (1 H, br).

Anal. Calcd. for C21H32ClN5O: C, 62.13; H, 7.95; N, 17.25. Found: C, 61.92; H, 7.94; N, 17.06.

EXAMPLE 7: 5-AMINO-6-CHLORO-*N*-{[1-(2,2-DIMETHYLPROPYL)PIPERIDIN-4-YL]METHYL}-2-METHYLIMIDAZO[1,2-*a*]PYRIDINE-8-CARBOXYAMIDE

The title compound was prepared according to the procedure described in the Step 6 in EXAMPLE 1, from 5-amino-6-chloro-2-methylimidazo[1,2-a]pyridine-8-carboxylic acid (EXAMPLE 1, Step 5) and {[1-(2,2-dimethylpropyl)piperidin-4-yl]methyl}amine (EXAMPLE 6, Step 2).

MS (ESI) m/z: 392 $(M+1)^+$.

m.p. (TG/DTA): 256°C.

IR (KBr) ν: 3302, 3144, 2951, 1638, 1605, 1564, 1543, 1516, 1433, 1321, 1285, 1267, 1231 cm^{-1}.

^{1}H-NMR (DMSO-d_6) δ: 0.82 (9 H, s), 1.23-1.42 (3 H, m), 1.60-1.64 (2 H, m), 2.01 (2 H, s), 2.12-2.19 (2H, m), 2.37 (3 H, s), 2.74-2.78 (2 H, m), 3.26-3.30 (2 H, m), 7.57 (2 H, br s), 7.85 (1 H, s), 7.87 (1 H, s), 9.92 (1 H, br).

Anal. Calcd. for C20H30ClN5O·0.1H2O: C, 61.01; H, 7.73; N, 17.79. Found: C, 60.67; H, 7.68; N, 17.53.

EXAMPLE 8: 5-amino-6-chloro-*N*-{[1-(3-methoxy-3-methylbutyl)piperidin-4-yl]methyl}2-methylimidazo[1,2-*a*]pyridine-8-carboxamide

Step 1. *tert*-butyl 4-({[(5-amino-6-chloro-2-methylimidazo[1,2-*a*]pyridin-8-yl)carbonyl] amino}methyl)piperidine-1-carboxylate

The title compound was prepared, according to the procedure described in the step 6 of EXAMPLE 1, from 5-amino-6-chloro-2-methylimidazo[1,2-*a*]pyridine-8-carboxilic acid (EXAMPLE 1, Step 5) and *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate (J. Prugh, L. A. Birchenough and M. S. Egbertson, *Synth. Commun.*, **1992**, *22*, 2357-60).

MS (EI) m/z: 421(M^+).

^{1}H-NMR ($CDCl_3$) δ: 1.06-1.84 (14 H, m), 2.44 (3 H, s), 2.58-2.85 (2 H, m), 3.45-3.49 (2 H, m), 4.00-4.22 (2 H, m), 5.84 (2 H, s), 7.34 (1 H, s), 8.17 (1 H, s), 10.17 (1 H, br t, J=5.7 Hz).

Step 2. 5-amino-6-chloro-2-methyl-*N*-(piperidin-4-ylmethyl)imidazo[1,2-*a*]pyridine-8-carboxyamide dihydrochloride

A mixture of *tert*-butyl 4-({[(5-amino-6-chloro-2-methylimidazo[1,2-*a*]pyridin-8-yl)carbonyl]amino}methyl)piperidine-1-carboxylate (EXAMPLE 8, Step 1, 15.1 g, 35.8 mmol) and conc. hydrochloric acid (5 mL) in 10% hydrochloric acid methanol solution (150 mL) was stirred at room temperature for 12 h. The solvent was removed to 30 mL *in vacuo* and to the residue was added diethyl ether (100 mL). Obtained precipitate was collected by filtration and washed with diethyl ether to give 13.9 g (98%) of the title compound as a pale yellow solid.

MS (ESI) m/z: 322$(M+1)^+$.

^{1}H-NMR (DMSO-d_6) δ: 1.39-1.53 (2 H, m), 1.80-1.91 (3 H, m), 2.45 (3 H, s), 2.69-2.89 (2 H, m), 3.22-3.26 (4 H, m), 8.38-9.13 (8 H, m).

Step 3. 5-amino-6-chloro-*N*-{[1-(3-methoxy-3-methylbutyl)piperidin-4-yl]methyl}2-methylimidazo[1,2-*a*]pyridine-8-carboxamide

The title compound was prepared according to the procedure described in the Step 5 in EXAMPLE 3 from 5-amino-6-chloro-2-methyl-*N*-(piperidin-4-ylmethyl)imidazo[1,2-*a*]pyridine-8-carboxyamide dihydrochloride (EXAMPLE 8, Step 2) and 1-iodo-3-methoxy-3-methylbutane*.

MS (ESI) m/z: 422 $(M+1)^+$.

m.p. (TG/DTA): 199°C.

IR (KBr) ν: 3499, 3325, 3182, 2926,1657, 1620, 1601, 1572, 1547, 1514, 1431, 1323, 1261, 1078, 721 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ: 1.16 (6 H, s), 1.37-1.49 (2 H, m), 1.60-1.72 (3 H, m), 1.82-1.86 (2 H, m), 1.91-1.99 (2 H, m), 2.35-2.40 (2 H, m), 2.46 (3 H, s), 2.95-2.99 (2 H, m), 3.18 (3 H, s), 3.43-3.47 (2 H, m), 5.03 (2 H, br s), 7.15 (1 H, s), 8.19 (1 H, s), 10.09 (1 H, br).

Anal. Calcd. for C21H32ClN5O2·0.2H2O: C, 59.27; H, 7.67; N, 16.46. Found: C, 59.00; H, 7.66; N, 16.19.

* Preparation of 1-iodo-3-methoxy-3-methylbutane

To a solution of 3-methoxy-3-methyl-1-butanol (3 g, 25.3 mmol) in dichloromethane (100 mL) were added triphenylphosphine (7.3 g, 27.9 mmol), imidazole (1.9 g, 27.9 mmol) and iodine (7.1 g, 27.9 mmol) at 0°C. The mixture was stirred at 0°C for 3 h. Aqueous sodium sulfite (5 mL) and aqueous sodium hydrogen carbonate (100 mL) were added and the mixture was extracted with dichloromethane (20 mL x 3). After removal of solvent, the residue was suspended to hexane and filtered. The filtrate was concentrated. Flash chromatography of the residue eluting with hexane/ethyl acetate (100 : 1) gave 684 mg (9%) of the title compound as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.15 (6 H, s), 2.11-2.17 (2 H, m), 3.15-3.21 (2 H, m), 3.18 (3 H, s).

R_f: 0.3 (hexane).

EXAMPLE 9: 5-amino-6-chloro-*N*-{[1-(3-methoxy-2,2-dimethylpropyl)piperidin-4-yl]methyl}2-methylimidazo[1,2-*a*]pyridine-8-carboxamide

Step 1. {[1-(3-methoxy-2,2-dimethylpropyl)piperidin-4-yl]methyl}amine

A mixture of isonipecotamide (1.0 g, 8.0 mmol), 3-methoxy-2,2-dimethylpropanoic acid (*Bulletin of the Chemical Society of Japan* **2001**, *74*, 1695-1702, 1.1 g, 8.0 mmol), 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU, 3.3 g, 8.8 mmol) and *N*,*N*-diisopropylethylamine (1.5 mL, 8.8 mmol) in *N*,*N*-dimethylformamide (8 mL) was stirred at room temperature for 18 h. Water (8 mL) was added and the mixture was extracted with ethyl acetate (20 mL x 6). Removal of solvent gave a crude of 1-(3-methoxy-2,2-dimethylpropanoyl)piperidine-4-carboxamide as a brown oil, which was dissolved in tetrahydrofuran (15 mL) and added to a suspension of lithium aluminum hydride (2.26 g, 47.7 mmol) in tetrahydrofuran (15 mL) at 0°C. The mixture was stirred at 40°C for 3 h and quenched with sodium sulfate decahydrate and potassium fluoride. Filtration through a pad of Celite and concentration of the filtrate gave 925 mg (54%) of the title compound as a colorless oil.

MS (ESI) m/z: 215 $(M+1)^+$.

^{1}H-NMR ($CDCl_3$) δ: 0.83 (6 H, s), 1.13-1.32 (2 H, m), 1.52-1.80 (3 H, m), 2.12-2.24 (4 H, m), 2.53-2.55 (2 H, m), 2.74-2.78 (2 H, m), 3.09 (2 H, s), 3.30 (3 H, s). A signal due to NH2 was not observed.

Step 2. 5-amino-6-chloro-*N*-{[1-(3-methoxy-2,2-dimethylpropyl)piperidin-4-yl]methyl}2-methyl-imidazo[1,2-*a*]pyridine-8-carboxamide

The title compound was prepared according to the procedure described in the Step 6 in EXAMPLE 1 from 5-amino-6-chloro-2-methylimidazo[1,2-*a*]pyridine-8-carboxylic acid (EXAMPLE 1, Step 5) and {[1-(3-methoxy-2,2-dimethylpropyl)piperidin-4-yl]methyl}amine (EXAMPLE 9, Step 1).

MS (ESI) m/z: 422 $(M+1)^+$.

m.p. (TG/DTA): 199°C.

IR (KBr) ν: 3309, 3152, 2922, 2868, 1638, 1603, 1560, 1545, 1512, 1425, 1321, 1111, 718 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ: 0.83 (6 H, s), 1.34-1.46 (2 H, m), 1.53-1.65 (1 H, m), 1.70-1.73 (2 H, m), 2.13 (2 H, s), 2.18-2.25 (2 H, m), 2.47 (3 H, s), 2.76-2.80 (2 H, m), 3.09 (2 H, s), 3.30 (3 H, s), 3.41-3.46 (2 H, m), 4.98-5.07 (2 H, m), 7.16-7.19 (1 H, m), 8.20 (1 H, s), 10.09 (1 H, br).

Anal. Calcd. for C21H32ClN5O2: C, 59.77; H, 7.64; N, 16.60. Found: C, 59.47; H, 7.65; N, 16.55.

All publications, including but not limited to, issued patents, patent applications, and journal articles, cited in this application are each herein incorporated by reference in their entirety.